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a systematic review

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EXECUTIVE SUMMARY

Background

Ovarian cancer is the seventh most common cancer in women world wide, and in England and Wales the mortality rate is 14.7 per 100, 000 females per year. Nearly half of all cases occur in women aged between 50 and 69, and in this age group the annual incidence of ovarian cancer is around 45 per 100, 000. The overall five-year survival rate is poor, at about 30%, with minimal improvement in this figure over the past 20-30 years. Survival is much better, around 75% at five years, for women whose disease is localised to the ovaries (FIGO stage I), but only about a quarter of cases in the UK are currently diagnosed at this stage. This has led to interest in methods to detect ovarian cancer in asymptomatic women, in the hope that population screening might result in earlier diagnosis and reduce mortality and morbidity from this disease.

The tests which have been most extensively evaluated as screening methods include ultrasound scanning, and the measurement of serum levels of CA125, a tumour marker produced by most ovarian cancers. When used for screening, CA125 measurement is followed by ultrasound scanning in women with abnormal CA125 levels ('CA125 based screening'). Women with persistently abnormal findings are then referred for diagnostic laparotomy or laparoscopy under general anaesthesia for removal of the ovaries.

The current status of the effectiveness of screening, and trials in progress

Deciding whether a screening programme should be established depends on the balance between the potential benefits of screening in terms of improved outcome for women with ovarian cancer; the harms of screening resulting from testing and investigating healthy women; and the resources required. The impact of screening on ovarian cancer mortality can only be reliably assessed by a randomised controlled trial (RCT) comparing similar groups of screened and unscreened women.

No RCTs of screening for ovarian cancer have been completed. This means that there is currently no reliable evidence that screening can improve outcomes for women with ovarian cancer (including those at higher risk from the disease). In the absence of evidence of effectiveness, it would be premature to establish any kind of screening programme.

Three large RCTs are currently in progress, two of which are based in the UK. One of the UK based trials is evaluating transvaginal ultrasound as a screening test, and the other CA125 based screening, with ultrasound as a follow-up test for women with elevated or rising CA125 levels. If successfully completed, in about 5-7 years' time these trials will provide evidence as to whether or not screening can reduce ovarian cancer mortality. They will also provide an estimate of the perioperative mortality and complication rates in women referred for diagnostic surgery. However, the trials

currently plan to provide little additional information concerning potential harms of screening, in particular the psychological impact of screening and the broader effects on morbidity of diagnostic surgery in false positives. One trial currently plans to provide an estimate of the cost-effectiveness of screening. The value of the information provided by these trials would be enhanced if an assessment of the relative cost-effectiveness of their different screening strategies was undertaken.

Screening test performance

Evidence relating to the performance of ultrasound scanning and CA125 as screening tests can be obtained from prospective screening studies. Such studies can provide information on intermediate outcomes such as detection rates, false positive rates and the stage at diagnosis of screen detected cancer. They cannot provide reliable evidence about the effectiveness of screening, which depends further on whether earlier detection and treatment results in improved outcomes. It should also be noted that the cut-off points and protocols used in these prospective studies varied widely; studies using the same screening test did not necessarily use the same criteria for defining positive results, and not all the studies specified the definitions of abnormal results; the full screening protocol was frequently not described fully. In addition, the conclusions regarding the impact of screening on stage distribution are based on the initial screening rounds (the prevalence screen); in these the proportion of early cancers may be lower than in subsequent screening rounds, and this may underestimate any benefit of screening.

Available evidence however suggests that both CA125 based screening and ultrasound screening can detect a higher proportion of ovarian cancers at stage I compared with that currently observed in the UK - around 50% diagnosed at stage I in CA125 based screening studies and around 75% in ultrasound screening studies. These data should be interpreted cautiously, however, because they are based on small numbers of cancers detected in diverse studies carried out mainly on self-selected women.

From the limited follow-up reported in published screening studies, annual screening with ultrasound appears to have a sensitivity close to 100%. The reported sensitivity of annual CA125 based screening is around 80%. The precision of these estimates is low, however, as they are based on small numbers of cancers.

The effect of different screening intervals on the detection rate and false positive rate has not been investigated. Less frequent screening may reduce the proportion of cancers detected at screening, but may also reduce the number of unnecessary investigations and the cost of screening. Intervals for ultrasound scanning of between one and three years are under investigation in the RCTs, while CA125 based screening has been carried out annually.

About 1.2-2.5% of women screened by ultrasound scanning have persistently abnormal findings resulting in referral for diagnostic surgery, but are found not to have ovarian cancer. The figure is lower for CA125 based screening, around 0.1-0.6%. Such diagnostic surgery carries a risk of complications such as infection, excessive bleeding,

and more seriously, damage to the bladder or bowel. There is also a small risk of death. These risks are difficult to quantify and give only a limited picture of the impact of false positive screening results, but perhaps 0.5-1% of women undergoing diagnostic surgery will suffer a significant complication. Most women referred for surgery who do not have ovarian cancer will be found to have a benign ovarian tumour or other benign gynaecological condition. The extent to which surgical intervention may benefit these women, by averting future clinical problems or perhaps reducing ovarian cancer risk, is unknown. There is however a risk that detection of benign and borderline tumours may become a target of ovarian screening, even though they would not have been associated with any morbidity during a patient's lifetime. Further research is required to determine whether this is the case.

The number of women finally classified as positive on screening and referred for diagnostic surgery is low compared with the number who initially have abnormal or equivocal test results. Perhaps 3-12% of screened women are recalled for further testing and assessment, resulting in potential distress and anxiety to otherwise healthy women, before they finally receive the reassurance of a negative result. There may be a lengthy period before this final decision is made.

The potential impact of screening for ovarian cancer

Typically, annual ultrasound screening of 10, 000 women aged 50-69 at average risk might result in 700 women being recalled for further assessment, 130 undergoing diagnostic surgery and 4 cancers detected (assuming 100% sensitivity) of which 2- 4 may be stage I (based on Table 4.3); a positive predictive value (PPV) of 3% for surgery and 0.6% for initial recall. Annual CA125 based screening might typically result in 300 women being recalled, 20 women undergoing diagnostic surgery and 3 cancers detected (assuming 75% sensitivity), of which 1-2 may be stage 1. This implies a PPV of 15% for surgery and 1% for initial recall.

The relatively low prevalence of ovarian cancer may limit the potential cost-effectiveness of general population screening. Compared to breast cancer, ovarian cancer causes around one third the number of deaths. This implies that to achieve comparable cost-effectiveness, screening for ovarian cancer would need to result in much greater relative reduction in mortality than breast screening (which reduces mortality by around 40% in screened women), or would need to be much less costly. If the optimum screening interval for ovarian cancer is less than 3 years, then the overall costs of any screening programme may be greater.

Comparing the performance of screening tests involves consideration of the balance between the detection rate, the false positive rate, and the costs. Evidence from prospective screening studies suggests that ultrasound screening is more sensitive than CA125 based screening, but that the latter method may result in a smaller proportion of false positives and hence a higher positive predictive value. However, a less sensitive test must be repeated more frequently to achieve the same overall detection rate of ovarian cancers, and this may reduce the apparent advantages of CA125 based screening. The screening method and interval resulting in the best overall balance of

potential benefits, harms and costs is currently unknown, but modelling studies suggest that annual CA125 based screening may provide lower overall benefits but at greater cost-effectiveness than annual ultrasound screening.

A number of potential improvements to screening tests are under development. It is suggested that the addition of colour Doppler imaging (CDI) to ultrasound screening may reduce the false positive rate, but mixed results have been reported. The additional impact of CDI on the sensitivity, false positive rates and costs of ultrasound screening requires clarification. The use of mathematical models, incorporating epidemiological data and CA125 levels, to determine thresholds for defining abnormal results has also been proposed, and is being evaluated in one of the RCTs in progress. Further developments of methods based on serological testing depend on the further evaluation of newer tumour markers. At present, none has been shown to improve overall performance compared with CA125 alone.

It is important that newly developed tests or screening strategies are evaluated in such a way that the findings can be related to the results of RCTs. This may mean increased use of study designs which directly compare the performance of different screening methods in the same group of women, since this increases the validity of the results. The impact of any newer methods on the overall cost-effectiveness of screening also needs to be considered.

Screening a higher risk population

A family history of ovarian cancer is one of the strongest risk factors for developing ovarian cancer. However, only about 7% of women with ovarian cancer report a family history of the disease. Most of these women have only one affected relative and are at only modestly increased risk, on average 2-3 times that of a woman with no family history. A small minority report more than one affected close relative. These women are at substantially increased risk, around 10 times that of the general population on average. This is equivalent to a 15% lifetime risk of developing the disease. Screening is currently being offered as a service in some UK centres to this latter group of women.

Screening women at higher risk does not alter the potential benefit of screening for each woman with ovarian cancer. The higher prevalence, however, means that fewer women need to be screened to detect each case of cancer, and there are fewer false positives for every case detected, increasing the positive predictive value. The balance of potential benefits, harms and costs may therefore be more favourable. The costs of identifying high risk women need to be taken into account, however, when considering the overall cost-effectiveness of this approach.

Until RCTs have been completed, there is no evidence as to whether screening women at higher risk is effective in reducing mortality. Further research is required before a full assessment of the potential benefits, harms and costs of screening can be made.

Until such information is available, it is premature to establish a screening programme, including services to seek out women at higher risk in order to offer them screening.

The results from RCTs in the general population could be used to model the impact of screening in different risk groups, if the natural history of ovarian cancer is similar. If, however, the disease progresses at a different rate in women at higher risk, the results may not be applicable. They will also be relevant only to the screening methods evaluated in the RCTs, and if different screening methods are proposed for higher risk women, comparison of their performance with the methods used in the trials will be necessary. Research in the higher risk group should therefore be directed towards areas in which there may be differences with the general population, such as the natural history, screening test performance, and the age-specific risks of developing ovarian cancer.

For some women with an extensive family history of ovarian and/or certain other cancers, the increased risk is associated with an inherited genetic mutation. The identification of some such mutations raises the possibility of testing individuals in these families to determine whether they are carriers, potentially enabling more accurate assessment of risk. This is not yet possible for many families, but this is a rapidly evolving field. Carriers of some specific mutations may have a lifetime risk of developing ovarian cancer as high as 50-60%, although there is little epidemiological data on which to base such risk assessments. Mutations frequently predispose to risk at several cancer sites and for some of these, screening tests of proven effectiveness are available. The implications of genetic testing for cancer risk are therefore broad, and go beyond the scope of this review. Consideration should be given to specific research to address the policy implications of these developments.

Conclusions: implications for policy and research

1. Screening for ovarian cancer is currently unproven as a strategy for improving outcomes for women with ovarian cancer. Screening programmes should therefore not be considered until further research provides a better understanding of the potential benefits, harms and costs involved. While awaiting the results of the current trials, demand for screening is likely to increase, and a strong national lead on this is required.

2. RCTs currently underway should, in 5-7 years, give an estimate of any impact of screening on ovarian cancer mortality. Information from the trials would be enhanced by extending their investigation of the adverse effects of screening, and by ensuring that comparisons of the cost-effectiveness of the different screening strategies evaluated can be undertaken.

3. Research into screening test performance has frequently been poorly reported, and has made insufficient use of designs which enable assessment of the relative performance of different test methods. Future developments to screening tests should be compared with the tests being evaluated in the trials, to enable an assessment of their marginal impact on potential benefits, harms and costs. Test

developments which require further evaluation include the marginal impact of adding colour Doppler imaging to ultrasound screening; the use of CA125 levels in multivariate algorithms to determine thresholds for ultrasound and surgical intervention; and the marginal value of adding CA125 measurement to ultrasound screening. It should also be noted that the screening modalitites reviewed in this report are continuously evolving; this makes evaluation difficult, and specification of the protocol particularly important. These modalities will require continuous re-evaluation in line with technical developments.

4. The relatively low prevalence of ovarian cancer means that the positive predictive value of screening tests, even those with very high specificity, is low. Since the consequence of a false positive result is a surgical procedure, consideration of the overall impact of ovarian cancer screening, and not only the potential benefits, is important. The low prevalence also limits the potential cost-effectiveness of population screening.

5. The balance of potential benefits, harms and costs of screening may be more favourable in the small group of women who are at significantly increased risk due to a strong family history. However, benefit from screening has not been established and therefore there is no case for establishing a screening programme in this group. No RCTs are planned in a higher risk population, but a screening study has recently been established. This will provide some evaluation of intermediate outcomes of screening, but may also increase demand for screening services.

6. Evidence of potential effectiveness of screening in women at higher risk could be extrapolated from the results of trials on women recruited from the general population. However, this will only produce valid results if the natural history of ovarian cancer is similar for these women, and for the screening strategies used in the trials. Research efforts should be directed towards evaluating the effectiveness and cost effectiveness of screening strategies for this higher risk group. This includes investigation of any differences in the natural history; the performance of screening tests compared with the strategies used in the RCTs; investigation of age-specific risk of developing ovarian cancer, and investigation of the psychological impact and value of risk assessment.

1 BACKGROUND

1.1 Objectives

The purpose of the review is to provide the NHS Health Technology Assessment (HTA) programme with an overview of the results of research evaluating screening for ovarian cancer.

The specific objectives of the review are:

- to evaluate the performance of the current screening tests for ovarian cancer
- to assess the adverse effects of screening, including morbidity associated with surgical intervention and the psychological morbidity associated with false positive diagnosis
- to report on the stage of development of newer methods of screening,
- to investigate the potential cost-effectiveness of screening in different risk groups

In addition, the review identifies the issues which need further research and the degree to which research in progress is likely to address these issues.

1.2 The size of the problem

Ovarian cancer is the seventh most common site for cancer in women world-wide and is most common in western industrialised countries. [1] In 1994 in England and Wales there were 3859 deaths due to ovarian cancer and in 1989, 5100 new registrations of the disease. [2,3]

1.3 Pathology

Ovarian cancer is not a single disease but represents a group of cancers arising from a variety of different cell types. Histological classification is complex but the majority of primary malignant tumours, around 90%, are of epithelial origin. [4,5] A distinct subset of tumours has pathological features intermediate between benign and invasive malignant disease and these are termed borderline tumours (also referred to as 'low malignant potential' tumours); they have a much better prognosis than invasive tumours.[5] Non-epithelial ovarian cancer includes germ cell tumours and sex cord stromal tumours. Germ cell tumours (which comprise around 3% of all ovarian cancers) arise at an earlier age on average, and have a better prognosis than epithelial ovarian cancers.

The focus of this review is on screening for invasive epithelial ovarian cancer, although some of the information discussed, particularly when derived from routine data sources, will relate to all primary ovarian cancers.

Box 1.1: FIGO 1986 staging system for ovarian cancer[6]

Stage	Definition
I	**Growth limited to the ovaries:**
IA	Limited to one ovary; no ascites; no tumour on external surfaces, capsule intact
IB	Limited to both ovaries; no ascites; no tumour on external surfaces, capsule intact
IC	Tumour either stage IA or IB, but with tumour on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
II	**Growth involving one or both ovaries with pelvic extension:**
IIA	Extension or metastases to the uterus or tubes
IIB	Extension to other pelvic tissues
IIC	Tumour either stage IIA or IIB, but with tumour on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes; superficial liver metastases; tumour limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum**
IIIA	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumour of one or both ovaries; histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter, nodes negative
IIIC	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes
IV	**Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastases equals stage IV**

1.4 Symptoms and treatment

Ovarian cancer tends to give rise to vague or non-specific symptoms such as abdominal discomfort, swelling due to tumour mass or ascites, menstrual irregularities or gastro-intestinal symptoms. The tumour spreads from the ovaries locally and also by peritoneal seeding, which can lead to widespread disseminated intra-abdominal disease. This intra-abdominal spread can occur when the ovarian tumour mass is small, and this, together with the insidious nature of the symptoms, means that the disease is frequently widespread at diagnosis. This has led to interest in the potential of screening, in the hope that identifying the disease prior to clinical presentation may increase the likelihood that treatment is effective.

The extent of spread of the disease at diagnosis is classified into four stages as shown in box 1.1. Establishing the stage of disease accurately requires extensive surgical exploration of the pelvis and abdomen.

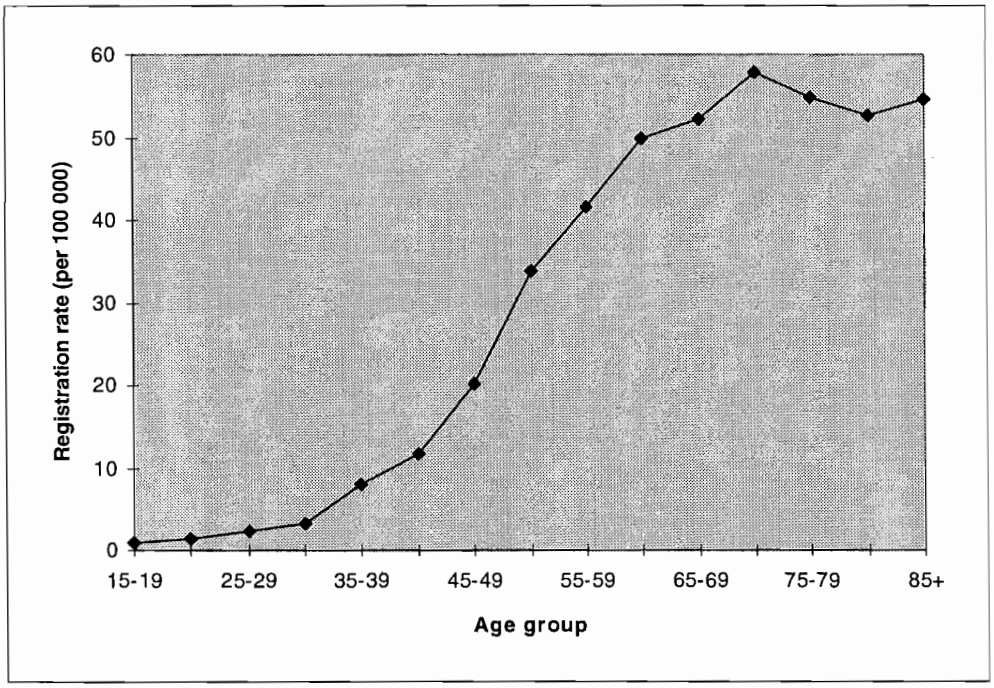
Treatment consists of surgical removal of as much tumour as possible, followed by adjuvant therapy if indicated. The usual treatment for stage I low grade disease is surgery alone, while more advanced disease may be treated with surgery followed by adjuvant chemotherapy.[6]

1.5 Incidence and mortality

The incidence of ovarian cancer can be estimated from the number of cancer registrations. The overall registration rate for ovarian cancer in England and Wales in 1989 was 19.7 per 100, 000 females.[3] The incidence of ovarian cancer is strongly related to age, and increases markedly over the age of 40; 94% of registrations occur in women over the age of 40, and 48% in women aged between 50 and 69 years. The registration rate in this age group is around 44 cases per 100, 000 per year (figure 1.1).

The mortality rate for ovarian cancer in 1994 was 14.7 per 100 000 females.[2] The mortality rate rises with age, and for women between the ages of 50 and 69, the mortality rate was 30 per 100, 000 in 1994. Approximately 1.3% of all deaths in women are due to ovarian cancer, the relative impact on mortality being greatest between the ages of 40 and 59 years, when around 5% of all deaths in women are attributed to ovarian cancer. Compared to breast cancer, the most common cancer in women, ovarian cancer results in one fifth as many cases per year and less than a third the number of deaths. [2,3]

Figure 1.1: registration rates for ovarian cancer in England and Wales[3]



The overall mortality rate from ovarian cancer in Great Britain has been stable over the past 20-30 years. [7,8] Within this, there has been a slight decrease in the mortality rate in women under the age of 55. An analysis of trends in survival in Scotland shows that survival in younger age groups has improved over the past few decades,[9] suggesting that the reduction in mortality may partly reflect improved treatment effectiveness.[8]

The number of deaths due to ovarian cancer in the future will be affected by the ageing of the population, the effectiveness of treatment, and changes in the prevalence of risk factors such as family size, oral contraceptive use and oophorectomy. The effect of trends in these factors may take some time to become apparent, and the overall impact on the mortality rate and the overall number of deaths is difficult to predict.

1.6 Survival

Overall 5-year survival for ovarian cancer in the UK is around 30%, and there has been minimal improvement in this figure over the past 20-30 years. [9,10]

Table 1.1 shows survival by stage from information from a number of population based cancer registries in the UK, which indicates current survival and proportions diagnosed at each stage within these populations. There is some variation in the reported survival rates and the proportion diagnosed at each stage. These variations may be due to a number of factors: variation in the completeness of staging data; variation in the population age structure, since younger patients present with earlier disease on average, and experience better stage-specific survival;[11] variation in practice of performing staging laparotomies and classifying the results;[12] and real differences between the populations in the proportion presenting early, and in the effectiveness of treatment.

The data show a consistent and strong relationship between stage at diagnosis and 5 year relative survival. The proportion diagnosed at stage I, where the tumour is localised to the ovaries, varies between 22% and 28%, and the 5 year survival for these cases varies between 72% and 81%. Survival for the majority of cancers which present at stages II-IV is much poorer. A similar picture is apparent in published data from international registries. [11,14,15]

This suggests that there may be scope for outcomes to be improved by increasing the proportion of cancers diagnosed early. However, it is possible that the observed survival advantage for early ovarian cancer reflects differences inherent in the tumour biology rather than the effectiveness of treatment. Clinically detected early cancers may be slower growing and have less propensity to become widely disseminated than those diagnosed at a more advanced stage. Screen detected early cancers may not have the same favourable characteristics and therefore may not demonstrate the same survival advantage observed for early cancers in an unscreened population.

Table 1.1: survival by stage and proportion diagnosed at each stage for selected UK regions

Registry (age range	Number of cases	Years diagnosed	Stage at diagnosis (%)	5 year survival by stage (%)
Thames (15-74 years)	4570	1986-90	I 28 II 21 III 3 IV 39 n/k 9	I 72 II 36 III 22 IV 13 n/k 48
East Anglia (all ages)	654	1989-91	I 22 II 8 III 39 IV 13 n/k 18	I 72 II 30 III 11 IV 2 n/k 14
West Midlands [13] (all ages)	1603	1985-87	I 22 II 4 III 33 IV 5 n/k 35	I 81 II 35 III 10 IV 7 n/k -
Scotland (35-64 years)	835	1987, 92-94	I 28 II 10 III 44 IV 15 n/k 3	I 77 II 49 III 17 IV 8 n/k 4
Scotland (all ages)	1829	1987, 92-94	I 23 II 9 III 45 IV 16 n/k 9	I 74 II 41 III 13 IV 3 n/k 2

The proportion of women with stage I disease who currently survive for 5 years is around 75% in the UK. If screen detected early cancers show similar survival rates, then even if screening could detect all cancers when they are localised, a significant proportion of women with ovarian cancer would not be 'cured'. However, a higher standard of staging and treatment might be achieved in a screening programme, and so survival rates might exceed those currently observed in an unscreened population. Clinical trials restricted to women with accurately staged low grade stage IA and IB disease have demonstrated long-term survival in excess of 90%.[16] However this may not be possible in the case of screen detected stage I disease.

1.7 Risk factors and aetiology

A wide range of risk factors has been postulated for ovarian cancer; [17,18] the most reliable information relates to reproductive factors, oral contraceptive use and family history (table 1.2).

An analysis of pooled data from 12 case-control studies performed in the US has investigated risk factors for invasive epithelial ovarian cancer.[19] These data showed a protective effect for pregnancy, with the risk reducing for each additional term pregnancy. Pregnancies ending in miscarriage or termination were also protective. Ovarian cancer risk also reduced with increasing duration of breast feeding.

Oral contraceptive use has consistently been reported to reduce the risk of ovarian cancer.[19-21] The risk appears to reduce with increasing duration of oral contraceptive use.[19] There is uncertainty over whether newer oral contraceptive formulations confer the same degree of protection as older, higher dose formulations. [19,20]

Women with a family history of ovarian cancer are at increased risk of ovarian cancer.[22] This is discussed further below. The contribution of each of these risk factors to ovarian cancer incidence depends both on the strength of the association and the prevalence of the risk factor in any given population. An analysis of data from the United States suggests that the most important risk factor on a population basis is the use of oral contraceptives; over half of all ovarian cancers in the US might be prevented if all women used oral contraceptives for at least 4 years.[23]

Table 1.2: Major risk factors for epithelial ovarian cancer

Risk factor	Relative risk/OR (95% confidence interval)
None	1.0
Oral contraceptive use[19]	0.66 (0.55-0.78)
Any term pregnancy[19]	0.47 (0.4-0.56)
One first or second degree relative with ovarian cancer[22]	3.1 (2.2-4.4)
Two or three relatives with ovarian cancer[22]	4.6 (1.1-18.4)

Based on these observations, it has been hypothesised that the suppression of ovulation, whether by pregnancy, breast feeding or the oral contraceptive pill, confers protection from ovarian cancer. This was first proposed by Fathalla, who hypothesised that 'incessant ovulation', and the subsequent trauma and healing of the ovarian epithelium, predisposed to malignant change.[24] An alternative hypothesis, that the high levels of circulating gonadotrophins associated with ovulation were responsible for inducing malignant change, has also been proposed.[25] Available epidemiological evidence is not wholly consistent with either of these hypotheses.[26]

1.8 Genetics of ovarian cancer

A family history of ovarian cancer in a first or second degree relative is one of the strongest risk factors for epithelial ovarian cancer. However, only about 7% of women with ovarian cancer report a family history of ovarian cancer disease.[27] Of these, the majority will have only one affected relative, while a small group of women, perhaps 1% of all women with ovarian cancer, will report a more extensive family history of ovarian and certain other cancers.[28]

Data from case-control studies suggest that the risk of ovarian cancer for a woman with one first degree relative with ovarian cancer is about 3 times the average risk.[22,27,29,30] Cohort studies of the incidence and mortality of ovarian cancer in

relatives of women with ovarian cancer, which are less susceptible to errors such as recall bias, indicate a slightly lower risk, about twice the risk compared with women with no family history.[31,32]

Data on the risk of developing ovarian cancer for women with more than one affected close relative are much more sparse, but is estimated at around 10-15% risk of developing the disease by age 70. [28,31] This is about ten times the risk in a woman with no family history.

In perhaps half of these families, the pattern of cancers will suggests the presence of a dominantly inherited gene conferring susceptibility to ovarian cancer and cancers at other sites. Three distinct clinical patterns of hereditary ovarian cancer are recognised. These are ovarian cancer with breast cancer; ovarian cancer with colorectal, endometrial, stomach and possibly pancreatic cancer (the 'Lynch II' syndrome); and site specific ovarian cancer syndrome.

Identification of the genetic mutations responsible for these syndromes is a complex and rapidly evolving field. Several predisposing genetic loci have been identified through genetic linkage studies. One of these, BRCA1, has been cloned and appears to act as a tumour suppressor. Mutations in this gene are thought to account for the majority of breast-ovarian cancer families, and also many apparently 'site-specific' ovarian cancer syndromes. It is estimated that carriers of the BRCA1 gene may have a risk of up to 60% of developing ovarian cancer by age 70. [33] A second gene associated with breast-ovarian cancer has also been identified, BRCA2, and also a number of genetic loci which may account for some of the 'Lynch II' families.[33]

The identification of these genes raises the possibility that eventually individuals in these families may be able to be tested to establish whether or not they have inherited the gene, and therefore to assess more accurately their risk of developing ovarian or other cancers. However, this is a complex and resource intensive process, and currently risk assessment is based mainly on a detailed family history.

2 SCREENING FOR OVARIAN CANCER

2.1 Principles of screening

The aim of screening is to reduce mortality and morbidity from ovarian cancer by detecting it at an earlier stage when treatment may be more effective. Any potential beneficial effect of screening is indirect, and depends on a causal chain of events. A screening test must be performed which indicates an increased probability of the disease; this must be followed up by further assessments to confirm the diagnosis leading to earlier treatment which must then result in improved survival.[34] Screening also has harmful effects, related to any risks of the screening and diagnostic process, and the extent to which women without the disease have abnormal test results leading to unnecessary further investigations. In particular, tumours of borderline malignancy may be diagnosed at screening which may not have been clinically detected during the woman's lifetime, and this may result in overtreatment. There is then the possibility that detection and treatment of such borderline malignancies becomes regarded as a goal in itself. In screening, because a healthy population is tested in order to detect the small proportion who have pre-clinical disease, any harms of screening may be experienced by a much larger number of people than the potential benefits. Deciding whether screening is worthwhile involves assessing the balance between the benefits and harms.

This balance of benefits and harms is related to the ability of a screening test to distinguish between women who have ovarian cancer and those who do not. This can be expressed as the sensitivity and specificity of the test. When the test is performed, four outcomes are possible (table 2.1): (i) the test correctly identifies women with the disease (true positive, a); (ii) the test is positive when in fact the woman is healthy (false positive, b); (iii) the test is negative when in fact the woman has cancer (false negative, c); and (iv) the test is negative and the woman does not have the disease (true negative, d). The sensitivity of the test expresses its ability to correctly identify women with the disease, and is calculated as the proportion of those with the disease who are detected on screening. The specificity expresses the test's ability to correctly identify healthy women, calculated as the proportion of those without the disease who screen negative.

Table 2.1: calculating the performance of a screening test

		Disease: *present*	*absent*	
Test:	*positive*	a	b	a+b
	negative	c	d	c+d
		a+c	b+d	a+b+c+d

Sensitivity (proportion of those with the disease testing positive) = a/a+c

Specificity (proportion of those without the disease testing negative) = d/b+d

A screening test which discriminates well between diseased and healthy women has a high sensitivity and specificity. The two parameters are however interdependent, and vary according to the threshold used to define a positive result. A low threshold, resulting in high sensitivity, will categorise more women without the disease as positive. A higher threshold will reduce the number of these false positives, increasing the specificity of the test, but at the expense of missing more women with the disease and therefore resulting in lower sensitivity.

Only women who have ovarian cancer which is detected by screening have the potential for their outcome to be improved. The magnitude of any potential benefits of screening depends on the extent to which treatment is more effective in these women, and on the sensitivity of the screening test to identify ovarian cancer. In a programme involving screening at regular intervals, the number of cancers detected by screening will further depend on the interval between each screening round, and the length of any preclinical phase of ovarian cancer. A rapidly developing cancer has less chance to be detected by screening at any given screening interval.

Screening is offered to otherwise healthy women who have not sought medical help, as they do in clinically presenting disease, and so there is a particular duty to minimise any harm done. The major sources of potential harms are any adverse effects of the screening tests, and the risks of unnecessary investigations in women with false positive results . The number of women affected in this way depends on the specificity of the screening test - the more specific the test, the lower the proportion of false positives.

The possible harms of screening are listed in Box 2.1. These can be described in terms of the psychological adverse effects, and the risks of morbidity or mortality associated with diagnosis. In the case of ovarian cancer screening, a proportion of women will be recalled for further assessment, most of whom will not have cancer, but who may experience a period of anxiety before being told that this is the case. Among this group there will be a small number in whom cancer will arise subsequently ("false negatives") and they may experience resentment and disillusionment. A number of women initially screened positive will need to undergo invasive investigations, with the associated risks of surgery, but will not be found to have cancer. A further group of women will have their cancer detected, but the prognosis will be unchanged despite earlier treatment; the harm for this group will be the extra time which they have had to live with a cancer diagnosis.

Assessing the value of a screening test involves balancing the harms and benefits experienced by different people. If there is no improvement in outcome for women with ovarian cancer detected on screening (true positives) then screening is clearly ineffective. If a beneficial effect is demonstrated, however, then this must be weighed against the magnitude of harmful effects and the number of women experiencing these effects. Finally, if the benefits are judged to outweigh the harms, then the resources

Box 2.1: Some factors influencing the benefits and harms of screening at a population level

Benefits depend on:	Harms depend on:
• Effectiveness of treatment for early disease compared with advanced disease • Ability of test to detect early disease (test sensitivity) • Screening interval and duration of preclinical phase of ovarian cancer • Prevalence of ovarian cancer in screened population • Size of target population • Uptake of screening	• Adverse effects of screening tests • Proportion of screened women recalled for further assessment • Anxiety/distress experienced by these women • Proportion of screened women undergoing diagnostic interventions (false positives - test specificity) • Morbidity/mortality experienced by these women • Size of screened population • Uptake of screening

needed to produce these benefits must be considered, because greater benefits might be obtained by using these resources in some other way.

The major determinants of resource use of a screening programme are the equipment, staff and training needed to set up and maintain the programme. The total direct costs will depend on the overall numbers and costs of the screening tests, follow-up tests and diagnostic tests, and these will be influenced by the screening frequency and the number of women invited for screening. This is not an exhaustive list; other potential costs include the establishment of national standard setting bodies, legal costs, the costs of holding official enquiries when standards are not met, and the cost of research into new methods. A full economic analysis should consider costs and benefits to the user as well as to the health service, and should compare a variety of screening options with the option of no screening.

Box 2.2: Examples of direct health service costs of screening and no screening options

Screened population	No screening
• Initial screening test (all women) • Repeated tests/secondary test (subgroup of women, may be multiple recalls) • Diagnostic surgery • Treatment of screen detected cancers • Diagnosis and treatment of cancers presenting clinically • Administration of follow-up and fail-safe procedures • Quality assurance & audit teams • Initial and continuing training • Costs of long-term follow-up of those with screen-detected abnormality	• Diagnosis and treatment of cancers presenting clinically • Possible treatment of benign conditions which may be averted by screening

2. 2 Evaluating screening

The potential benefits and harms of screening can only be reliably estimated in a RCT. This allows a direct measurement of the effect of screening on the length and quality of life, by comparing a screened and an unscreened population who are otherwise similar.

Prospective screening studies, which resemble the intervention arm of an RCT but have no control group for comparison, can be used to measure outcomes which only occur in screened populations. These include the false positive rates, and the outcomes experienced by these false positives. With adequate follow-up, such studies can also estimate the sensitivity of screening at varying screening intervals. The costs of screening can also be estimated. However, these studies cannot be used to evaluate potential benefits of screening. This is because survival may appear to be improved in screened women simply because cancer has been detected earlier (lead time bias). Furthermore screening may preferentially identify slower growing tumours which have an inherently better prognosis (length bias).

In the absence of direct evidence about the benefits of screening, indirect evidence may be used to estimate possible benefits in a model of screening. This involves using data on the sensitivity and specificity of the screening tests, the effect of screening on stage at diagnosis, the effect of earlier treatment, and so on. Since many assumptions must

usually be made in constructing such models they may be inaccurate, and the effect of these assumptions made should be investigated with sensitivity analyses.

Deciding whether screening is worthwhile depends on the overall benefits and harms of screening, and the resources required. Various ways of summarising this information are possible, for example by calculating the costs per life saved, the costs per life year gained, or the costs per quality adjusted life year. These methods subtract negative effects on health from the positive effects on health to obtain an overall summary of health outcomes 'produced' by screening. It may also be helpful to consider positive and negative effects separately, to enable an assessment of the distribution of benefits and harms. Screening may result in large benefits for a small number of people, with larger numbers affected by smaller negative effects.

There may also be a range of opinions among women and health professionals concurring the balance of benefits and risks for which they would consider screening worthwhile, and forming a policy about screening needs to take account of these different perspectives

2.3 Screening methods for ovarian cancer

a. Ultrasonography

Ultrasonography uses imaging of the ovaries to detect changes in size and shape which may indicate abnormality. Ultrasound scanning may be performed transabdominally or transvaginally. The size of ovaries measured by the two techniques is similar but more detail of the ovarian morphology can be obtained using the transvaginal route, and this has become the preferred method.[35,36] The transvaginal route also removes the need for women to have a full bladder on scanning, which may increase acceptability. Ultrasonography is carried out by trained technicians, radiographers or physicians, and on average each examination takes around 15 minutes.[37] Because ultrasound scanners are expensive and bulky, examination takes place at a central facility where the scanner is installed.

Changes in size and shape of ovaries can be transient or reflect normal physiological events, particularly in premenopausal women. After the menopause the ovaries are smaller and tend to reduce in size with age.[36] Criteria for defining an abnormally enlarged ovary therefore vary with menopausal status and age.

Persistently enlarged or abnormal looking ovaries can occur as a result of benign or malignant tumours or tumour-like conditions. There are no universally accepted criteria for distinguishing between benign and malignant conditions on the basis of ultrasound findings, although many authors have described systems for classifying morphological abnormalities,[38,39] and some have attempted to derive numerical scoring systems which would provide a more objective way of identifying ovarian malignancies.[40] Common parameters included in such classifications include the size of the ovary, the number of locules in cystic masses, and the uniformity of echogenicity of solid masses. Some types of abnormal morphology, such as papillary projections into a

cyst are considered highly suspicious,[39] while many simple cysts either resolve or remain stable over long periods.[41]

A more recent technique which may be of use in distinguishing between benign and malignant ovarian abnormalities is the use of colour Doppler imaging. This is used in conjunction with grey-scale ultrasonography, and enables visualisation of ovarian blood vessels and characterisation of the pattern of blood flow. Malignant tumours induce the formation of new blood vessels, and these vessels appear disorganised and have reduced smooth muscle in their walls, leading to reduced resistance to blood flow and high flow velocity. A variety of methods can be used to calculate the velocity of blood flow, but there is wide variation in the extent to these methods have been found useful for discriminating benign from malignant masses.[42]

b. CA125

CA125 is a glycoprotein produced by some ovarian cancers.[43] Levels of CA125 in serum can be measured by means of a blood test and laboratory assay of the serum. The test can therefore be carried out in any suitable location and by any personnel trained in venepuncture.

Elevated levels of CA125 have been reported in 61- 96% of all clinically diagnosed epithelial ovarian cancers, and in 29 -75% of cancers diagnosed at stage I.[44] Elevated levels have also been reported in other malignancies, for example endometrial and pancreatic cancer, and in a variety of benign gynaecological conditions, such as endometriosis, uterine leiomyoma (fibroids) and pelvic inflammatory disease.[45] CA125 levels in healthy women vary with menopausal status and past history of hysterectomy.[46]

Studies of CA125 levels in stored blood samples from population based serum banks and observational cohort studies indicate that raised CA125 levels can occur many years before the clinical diagnosis of ovarian cancer; furthermore, over 95% of women who do not develop ovarian cancer do not have elevated levels of CA125. [47-51] Measurement of serial levels of CA125 suggests that women with ovarian cancer demonstrate rising levels, whilst elevated levels associated with other conditions may remain stable over time.[52]

When used for screening for ovarian cancer, CA125 measurement is used in conjunction with ultrasound. Ultrasound may be performed at the same time as blood is taken for CA125, or women with elevated or rising CA125 levels may be recalled for ultrasound scanning.

c. The screening process

Screening for ovarian cancer involves a number of stages. The initial test, either ultrasound or CA125, is performed on all women. The findings of this initial screening test then determine whether the woman is recalled for further assessment, which may

consist of a number of further stages. The initial test may be repeated one or more times, to establish whether abnormalities have resolved, and a secondary test may be performed, such as ultrasound screening with colour Doppler imaging, or ultrasound screening following initial CA125 measurement. Women who have persistent abnormal findings at the end of this process are then referred for a definitive diagnosis to be made. For ovarian cancer, this involves an invasive surgical procedure, usually an open or laparoscopic oophorectomy. This enables ovarian tissue to be removed and examined histologically to confirm whether or not a malignant tumour is present. Women diagnosed with ovarian cancer will then require further surgery for accurate staging of the disease and removal of tumour mass. Treatment may also involve chemotherapy or other adjuvant therapy.

3 METHODS

3.1 Sources

The review was carried out using structured guidelines for systematic reviews.[53] A comprehensive search for studies and reviews evaluating screening tests was conducted to address the main objective of the review - assessment of the performance of screening tests. Supplementary searches were performed specifically to address the additional objectives.

i) Evaluation of screening test performance

A sensitive search strategy for studies evaluating screening tests was used (see appendix 1). The following databases were searched: Current Contents, MEDLINE (1966-May 1997), computerised EMBASE (1982 - May 1997), the nursing database CINAHL, the Cochrane Register of Controlled Clinical Trials, and CANCERLIT (to May 1997). Researchers and experts in the field, and consultants to the review were also contacted to identify any unpublished studies. In addition, the bibliographies of literature reviews in the area were used as sources of relevant studies. Conference proceedings were identified through CANCERLIT.

ii) Assessing the adverse effects of screening

This involved a search of MEDLINE (1982-1997) EMBASE (1982-1997), the nursing database CINAHL, and PSYCHLIT (1974-1997). Two search strategies were used, one to identify case series of surgical procedures similar to the diagnostic procedures used in screening for ovarian cancer, and the other to identify research on the psychological aspects of screening (Appendix 1).

iii) Investigating screening methods under development

Formal systematic review procedures were not felt to be appropriate to address this issue. Relevant information was identified from three sources:

1. Authors of all the studies identified in the main review, and other researchers in the field were contacted to obtain information on new developments.
2. A major international workshop (Ovarian Cancer Screening International Meeting, Royal College of Obstetricians and Gynaecologists, 21-22 April 1997) was attended.
3. Data were also extracted from relevant abstracts identified during the main search for studies evaluating screening tests.

On the basis of these consultations, a view of the likely future developments in this field was obtained.

iv) Assessment of the cost-effectiveness of screening for ovarian cancer

Searches for economic evaluation studies were conducted in ECONLIT, MEDLINE, and the NHS Economic Evaluation Database (Appendix 1). In addition, studies reporting cost information were identified from the main search.

3.2 Inclusion criteria

(i) Evaluation of the performance of screening tests

Studies which prospectively evaluated a test or a combination of tests to detect ovarian cancer in asymptomatic women were eligible for inclusion. Three criteria were used to define studies eligible for inclusion:

1. The women included in the study should be asymptomatic (i.e. not presenting clinically with symptoms suggestive of ovarian cancer)
2. The test should be carried out before the diagnosis is known
3. Women testing positive should be followed up with diagnostic surgery to establish whether they have ovarian cancer

Only prospective screening studies were included, so that estimates of sensitivity and specificity would be directly applicable to the use of the test in a screening situation. RCTs of screening were also eligible for inclusion under these criteria.

Many studies have evaluated the performance of these tests in detecting cancer in women already scheduled for surgical investigation. However, because these studies include women with clinically apparent ovarian abnormalities, they are likely to over-estimate sensitivity compared with the use of the test in asymptomatic women. This type of study was therefore excluded from the review.

Three reviewers independently assessed the retrieved abstracts and titles for relevance, and the full versions of selected papers were independently assessed for inclusion by two reviewers. Multiple publications of single studies were included only once, with relevant data extracted from several separate papers where necessary. Studies in any language were considered for inclusion.

ii) Assessing the adverse effects of screening

Studies eligible for inclusion were those reporting information on the surgical complications of procedures used in diagnosing ovarian cancer, for example open or laparoscopic oophorectomy, and studies reporting the psychological outcomes of screening for ovarian cancer. These studies were identified both from the main search for studies evaluating screening tests, and also from the specific searches outlined above.

As the literature on psychological adverse effects was known to be very limited, any study reporting psychological effects of ovarian cancer screening in the general

population or in high risk women was included. With respect to adverse effects of surgery, only studies with more than 50 patients are included (e.g. case series reporting complications associated with oophorectomy, or large comparative studies). Studies of oophorectomy carried out at the same time as hysterectomy, and studies of the long term effects (e.g. osteoporosis and depression) of oophorectomy were excluded.

iii) Assessment of the cost-effectiveness of screening for ovarian cancer

Any study reporting cost data for ovarian cancer screening was eligible for inclusion. This included economic evaluations, cost-effectiveness studies (including cost-minimisation and cost-consequences analyses), cost-benefit analyses and costing studies. In addition, any cost data reported in studies of the performance of screening were recorded.

3.3 Data extraction and assessment of study validity

Data were extracted from studies meeting the inclusion criteria by one reviewer using a standard data extraction form and checked by a second reviewer. Where appropriate, authors were contacted for additional data. Information was extracted from each study relating to the study population, all relevant details of the screening protocol, methods of follow-up, and the outcomes of screening in terms of the number of women recalled, the number screened positive, and the number with ovarian cancer. The data extraction form is given in appendix 2.

These data were then used to calculate summary statistics for each study: the prevalence of cancer detected in the screened population, the sensitivity, specificity, and the probability of having ovarian cancer at diagnostic intervention (i.e. the positive predictive value, or PPV) and the false positive and recall rates.

Information was also recorded relating to the methodological quality of each study, based on criteria recommended by the Cochrane Methods Working Group on systematic review of screening and diagnostic tests.[54] Information relating to the following methodological issues was recorded:

- the method and completeness of follow-up of women screened negative, which affects the reliability of estimates of false negatives and hence test sensitivity
- the clarity of cut-off points and explicitness of the description of the protocol. This affects the generalisability of the study and may also influence the reliability of the estimates of the outcomes of screening (numbers of true and false positives, etc.)
- the completeness of result reporting including drop-out rates at each stage of screening. This affects the reliability of the estimates of the outcomes of screening, particularly the false positive rates if a significant proportion of women have not completed the screening process at the time of reporting.
- the description of study population with respect to major risk factors. This may affect the generalisability of the results to other populations.

These quality criteria were not used to obtain an overall quality score, because they affect the validity of different aspects of the study (for example, the quality of the follow-up of women screened negative influences primarily the estimate of test sensitivity). Instead, these factors were considered separately in assessing the validity of each study in relation to the different outcomes investigated.

4 RESULTS FROM PUBLISHED STUDIES

4.1 Studies identified

25 separate prospective studies of ovarian cancer screening in apparently healthy women were identified which fulfilled the inclusion criteria. Studies which were assessed and judged not to meet the review's inclusion criteria are listed in appendix 3. The most frequent reasons for exclusion of studies were that the women screened were not asymptomatic (7 studies) or that the study was not a prospective investigation of test performance, with definitive diagnosis in those testing positive (20 studies). Eleven articles were excluded because they duplicated publication of data relating to the same women.

All of these 25 studies were prospective screening studies, where women were screened for ovarian cancer but there were no comparisons made with unscreened women. Details of the study designs and results are given in appendix 4. The search also identified three on-going RCTs of screening: no results have so far been published.

4.2 Appraising the information available from prospective screening studies

Uncontrolled screening studies cannot provide reliable evidence concerning the effect of ovarian cancer screening on health outcomes such as mortality and quality of life. However, outcomes which only occur in screened women, such as the risks of screening, can be measured, together with information about the performance of the screening tests in discriminating between women with and without cancer.

Measurement of the sensitivity and specificity requires comparison of the screening test against the best available reference standard for the diagnosis of ovarian cancer - the histological examination of ovarian tissue removed from the woman. However, this itself is subject to inter- and intra observer variability in interpretation. Also, since the histological examination involves an invasive procedure, in a screening study performed on apparently healthy volunteers, this information can only be obtained for those testing positive. Therefore only the numbers of true and false positives can be directly measured with reference to histological diagnosis. The numbers of true and false negatives cannot be directly observed at the time of screening, but can be estimated by following up women who have screened negative and measuring the subsequent occurrence of ovarian cancer. This is illustrated in figure 4.1. The number of 'false negatives' therefore increases with increasing duration of follow-up, and the sensitivity estimates obtained measure the ability of screening to detect cancers which would otherwise become clinically apparent within a defined time period. It is not possible to distinguish whether these false negatives were present at the time of screening, or developed some time after screening.

The accuracy of the estimate of sensitivity and specificity obtained from these studies depends on the completeness and accuracy of the data reported. The boxes with broken lines in figure 4.1 indicate the points at which incomplete follow-up data can introduce inaccuracies into the estimates of sensitivity and specificity. If a large proportion of women do not complete the screening process, either because they have chosen not to attend or because at the time of reporting the study they are still undergoing further tests, then the estimates of true and false positive rates will be inaccurate. Similarly, the quality of follow-up of women screened negative will affect the accuracy of estimates of the number of false negatives.

Figure 4.1 also illustrates the various stages of the screening process: the application of an initial screening test does not lead directly to diagnostic surgery, but is preceded by an intermediate stage at which women with an initial positive or equivocal test result are recalled for further assessment. This further assessment may involve a number of repeated tests, or the use of different tests, before a final decision is made on whether to refer the woman for surgery. Women undergoing further assessment may experience considerable anxiety as they await the results of further tests, and therefore the proportion of women affected in this way needs to be considered when assessing the impact of screening. Repeated tests will also add to the costs of the screening process.

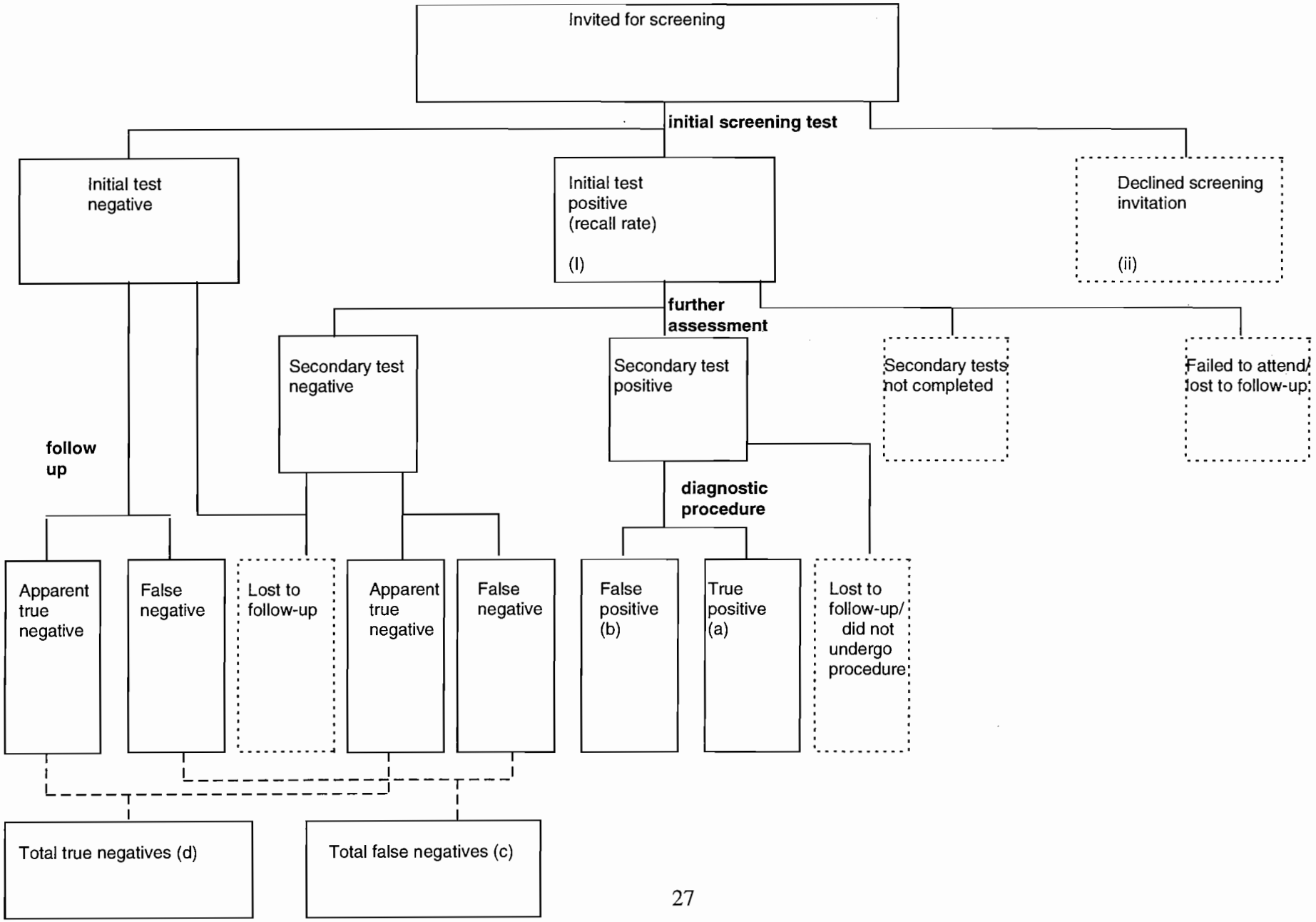
4.3 Study populations and sample size

Of the 25 studies identified, 16 screened women at average risk for their age of developing ovarian cancer, and therefore their results may be relevant to general population screening. These studies used a variety of recruitment methods. Two invited a random sample from a population register, [55,56] while a further two invited women already attending other screening programmes. [36,57] These studies reported uptake rates for screening of between 50 and 74%. The remaining studies mainly recruited self selected volunteers who responded to publicity about the study, or did not state their recruitment methods. Such studies do not allow calculation of an uptake rate or assessment of the extent of selection bias, and if their subjects differ from the general population in their risk of ovarian cancer the results may be misleading.

The 16 general population studies all stipulated a lower age limit for eligibility, which ranged from 18 to 55 years, but was most frequently either 45 or 50 years. Several studies restricted entry to post-menopausal women, and some had other exclusion criteria, such as previous hysterectomy (see appendix 4).

Of the 9 further studies recruiting women at higher than average risk of developing ovarian cancer, 7 investigated screening in women with a family history of ovarian or certain other cancers. The precise inclusion criteria varied for each study. These studies included younger women on average than the general population studies. All the studies on women with a family history were carried out on volunteers responding to publicity or referred by their doctors.

Figure 4.1


Invited for screening
initial screening test
Initial test negative
Initial test positive (recall rate)
(I)
Declined screening invitation
(ii)
further assessment
Secondary test negative
Secondary test positive
Secondary tests not completed
Failed to attend/ lost to follow-up
follow up
diagnostic procedure
Apparent true negative
False negative
Lost to follow-up
Apparent true negative
False negative
False positive (b)
True positive (a)
Lost to follow-up/ did not undergo procedure
Total true negatives (d)
Total false negatives (c)

The size of the studies varied between 435 and 22, 000 women for general population samples, and between 137 and 1601 for studies on high risk populations. The median size of study carried out in a general population was 2572 women. If the incidence of ovarian cancer in this type of population is around 1 in 2500 per year (comparable to that in England and Wales for women over age 40), then a study of this size would expect on average to detect perhaps 1 or 2 cancers on initial screening.

4.4 Screening methods

The studies identified evaluated a wide variety of screening tests and combinations of tests. Table 4.1 shows the number of studies using each method of screening.

Table 4.1: Number of studies using each screening method

Screening method:		Number of studies:	
Initial screening test	**Follow-up test***	**General population**	**High risk population**
TAS/TVS	-	6	1
TVS with CDI	-	2	1
TVS	CDI	1	1
TVS	FNA/B	1	-
TVS	CA125 or other markers	2	-
CA125	TVS/TAS	4	-
TVS with CA125	-	-	6

*test performed only on women with positive result on initial test for further assessment; women positive on follow-up testing referred for diagnostic surgery
TAS: trans-abdominal sonography; TVS: trans-vaginal sonography; CDI: Colour Doppler imaging; FNA/B: fine needle aspiration cytology or biopsy.

In addition, four studies also included a comparison with pelvic examination.[58-61]

Studies using the same modality of screening test did not necessarily use the same criteria for defining positive results. Most of the studies using grey-scale ultrasound (TAS or TVS) as an initial test used a combination of ovarian volume and morphological criteria to define abnormal results, although there were differences in the detailed definitions of abnormalities. For colour Doppler, there was much less consistency in the criteria used to define positive results, with a variety of parameters and cut off points used, including pulsatility index, resistance index, and peak systolic flow. Studies using CA125, followed by ultrasound scanning in those with elevated levels ('CA125 based screening'), used either 30 U/ml or 35 U/ml as cut-off for abnormal result. Not all the studies specified the definitions of abnormal results or the full screening protocol used (Appendix 4).

The studies showed considerable heterogeneity both in the study populations and in the screening tests they used. Furthermore, many studies did not permit measurement of

test sensitivity (see below). It was therefore considered inappropriate to attempt to calculate pooled measures of the performance of the various screening tests, or to construct summary receiver operating curves. Instead, a qualitative summary of the findings will be given, including a discussion of the validity of the individual studies.

4.5 Sensitivity of screening tests

The sensitivity of a screening test is the proportion of women with cancer (true positives and false negatives) who are correctly identified by the test. As discussed in section 4.2, in this type of study the number of cases missed can only be estimated by follow-up of women screened negative to see if they subsequently develop clinical ovarian cancer.

Of the 25 screening studies identified, only six reported a method for follow-up of those screened negative which was reasonably complete (over 85% response) at least one year after screening. [35,56,60,62,64] The details and results of this follow-up, and the estimated sensitivity of screening, are given in table 4.2. Information is also given for three further studies which reported cancers arising in screen negative women, or who stated that no such cancers had arisen, but did not describe the method or completeness of follow-up. [36,59,65]

Pooled estimates of sensitivity are not given because it is inappropriate to consider sensitivity without reference to the specificity achieved, since the two parameters are interdependent.[54] Furthermore, each study used either a different screening method, or recruited different populations. The individual sensitivity estimates were also very imprecise. For these reasons a summary receiver operating curve was not constructed to summarise test sensitivity and specificity.

No studies using ultrasound as an initial test reported any ovarian cancers arising clinically within 1 year of a negative screen. Two such studies followed women up for more than one year, and these both reported cancers arising clinically at 24 months after screening. [35,56] One of these reported follow-up information at 4 years, which indicated a sensitivity of 60%.[35] One study reported the results of three screening rounds at approximately 18 month intervals, and reported no interval cancers.[62]
The small size of the studies and the lack of long-term follow-up limits the conclusions that can be drawn regarding test sensitivity. However, it appears that significant numbers of interval cancers arise in the first year following CA125 screening, while for ultrasound, interval cancers have appeared around 18 months after screening. The suggestion that ultrasound screening is more sensitive than CA125 followed by ultrasound is supported by one study which has directly compared the performance of these two screening methods in the same cohort of women.[66] This is much more valid than comparisons between different studies, because it eliminates differences due to the characteristics of the women - in effect, each woman acts as her own control. In this analysis, three of the six cancers (one out of three invasive tumours and two out of three borderline tumours) would have been missed using a CA125 cut off of 30U/ml or 35 U/ml as an initial screen, suggesting that at least in this population of women with a family history of ovarian cancer, ultrasound is considerably more sensitive.

Table 4.2: sensitivity of screening tests at 1 year follow-up

Study	Sample	Test	Cancers detected at screening	Method of follow-up	Cancers arising in women screened negative	Sensitivity after 1 year follow-up (Exact 95% CI)
Campbell[62]	5479 Aged >45 or with family history	TAS	5 (after 3 screening rounds)	89% women contacted at 1 year	None	100% (48-100)
Vuento[56]	1364 Aged 56-61 eligible for mammography screening	TVS+CDI	1	Finnish cancer registry	None at 1 year 1 at 2.5 years	100% (3-100)
Bourne[35]	1601 Family history of OC, mean age 47 (range 17-79)	TVS then CDI	6	100% women contacted between 6 and 16 months following screening	None at 1 year 4 at 4 years	100% (54-100)
Schincaglia[64]	3541 Post-menopausal aged 50-69	TVS then FNA	2	Cancer registry and annual questionnaire - 100% complete	None at 1 year	100% (16-100)
van Nagell*[65]	8500 50+ and post-menopausal, or 25+ with family history	TVS	8	not stated	1 at 1 year (discovered at surgery)	88% (47-100)
Parkes*[36]	2953 Aged 50-64	TVS then CDI	1	not stated	None at 1 year 1 at 19 months	100% (3-100)
Jacobs[60]	1010 Postmenopausal aged 45+ (mean 54)	CA125 then US	1	postal questionnaire, 100% response	None at 1 year	100%
Jacobs[63]	22 000 Postmenopausal aged 45+ (median 56)	CA125 then US	11	postal questionnaire 99% response at 1 year, 57% at 2 years	3 at 1 year 8 at 2 years	73% (39-94)
Adonakis*[59]	2000 Aged 45+ (mean 58)	CA125 then US	2	not stated	None at 1 year	100% (16-100)

*studies with poor details of follow-up

TAS: trans-abdominal sonography; TVS: trans-vaginal sonography; CDI: Colour Doppler imaging; FNA/B: fine needle aspiration cytology or biopsy.

Because of the limited follow-up information, and the fact that only one study has reported results for successive screening rounds, little can be inferred about appropriate screening intervals or the natural history of ovarian cancer. A more sensitive screening test is likely to require less frequent screens to detect the same proportion of cancers. The rate of appearance of clinical ovarian cancer following screening in these studies suggests that screening intervals between one and perhaps 3 years merit further investigation.

4.6 Stage at diagnosis of screen detected cancer

Measures of test sensitivity do not necessarily indicate the likelihood or extent to which screening will detect cancers earlier. A more significant observation would be an increase in the proportion of cancers detected at an early stage. Although this would not in itself demonstrate that screening is effective, evidence to the contrary would suggest that screening is unlikely to improve outcomes.

Table 4.3 shows the stage distribution of the cancers detected in the general population screening studies. One study is excluded because stage at diagnosis was not reported.[67] The individual studies are relatively small and each detected only a few cancers, and therefore the confidence intervals for the proportion diagnosed at stage I are extremely wide. A more precise estimate can be obtained by calculating the average proportion diagnosed at stage I; this is shown in table 4.3 separately for ultrasound based screening and for CA125 based screening. 50% (95% CI 23-77) of cancers detected in studies using CA125 followed by ultrasound were at stage I, and 61% (95% CI 38-80) in studies using ultrasound as an initial screening test. In comparison, data from cancer registries indicates that in the largely unscreened UK population, the proportion of cancers diagnosed at stage I is around 22-28%. This suggests that the evidence is consistent with some improvement in stage at diagnosis for screen-detected cancers, which may be greater for ultrasound based screening.

A number of issues should be considered in assessing the significance of these findings. The first time a population is screened, the stage distribution will reflect the prevalence of advanced and early cancers in the population, and therefore the proportion of early cancers may be lower than in subsequent screening rounds. Therefore, in an attempt to ensure comparability, only studies reporting initial screening rounds have been included in the above calculation, and this might underestimate the potential impact of repeated rounds of screening on stage at diagnosis. Not all studies explicitly stated that they were only reporting prevalence screening and it is therefore possible that some results relate to several screening rounds reported together. Furthermore, an accurate estimate of the stage shift resulting from screening should include all the cancers arising in the screened population, including those 'missed' by screening. This was not possible due to the limited follow-up information available.

Table 4.3: Stage at diagnosis and prevalence of screen-detected cancer in general population studies

	Number screened	Number of cancers (of which borderline tumours)	Prevalence of screen-detected cancer (95% CI) per 100 000	% diagnosed at stage I (95% CI)
Ultrasound based screening:				
Goswamy[68]	1084	1	92	100
Millo[57]	500	0	0	-
Campbell[62] (first screen)	5479	2 (1)	36	100
Demidov[69]	11 996	11	91	36
van Nagell[65]	8500	8	94	75
Tabor[55]	435	0	0	-
Kurjak[70]	5013	4	80	100
Vuento[56]	1364	1 (1)	73	100
Parkes[36]	2953	1	34	100
Schincaglia[64]	3541	2	56	0
Holbert[71]	478	1	210	100
*All ultrasound studies which appear to report only prevalence screen**	*32 843*	*23 (2)*	*70 (41-98)*	*61 (38-80)*
*All ultrasound studies where it is clear that only the prevalence screen is reported***	*15 834*	*8 (2)*	*51 (16-90)*	*75 (35-97)*
CA125 followed by ultrasound:				
Jacobs[60]	1010	1	99	100
Jacobs[63]	22 000	11	50	36
Grover[61]	2550	0	0	-
Adonakis[59]	2000	2 (1)	100	100
All CA125 studies	*27 560*	*14 (1)*	*51 (24-78)*	*50 (23-77)*

* excludes van Nagell. ** excludes van Nagell, Demidov, Kurjak

Many of these studies gave few details of their recruitment methods, making it difficult to assess whether the women were truly representative of the general population. If women presenting for screening who had signs suspicious of cancer were excluded from the reported results of screening, or if women with more advanced cancers were less likely to volunteer for the studies, the proportion of screen detected cancers diagnosed at stage I may be misleadingly high.

A further potential source of error is the classification of borderline tumours. These are tumours with features intermediate between benign tumours and frankly invasive cancers; they have a good prognosis, are more likely to be detected at an early stage, and are not thought to be precursors to more aggressive cancers. The classification of borderline tumours varies, and therefore the screening studies may not have reported them in a comparable way. The proportion of screen detected cancers reported to be borderline tumours was however less than 10%, suggesting that the overdiagnosis of such tumours may not be a significant problem. Excluding such tumours slightly reduces the proportion of screen-detected stage I cancers.

Table 4.4: Stage at diagnosis and prevalence of screen-detected cancer in studies screening women at high risk

	Number screened	Risk group	Number of cancers (of which borderline tumours)	% diagnosed at stage I (95% CI)
Ultrasound screening:				
Andolf[58]	805	OPD attenders	3 (2)	67
Bourne[35]	1601	family history	6 (3)	83
Weiner[72]	600	history of breast cancer	3	33
Ultrasound with CA125:				
Karlan[73]	597	family history	1 (1)	100
Muto[74]	384	family history	0	-
Schwartz[75]	247	family history	0	-
Dorum[76]	180	family history	7 (3)	43
Belinson[77]	137	family history	1	0
Average for all studies	*4551*		*21 (9)*	*57 (34-78)*
Average for all studies on women with a family history	*3146*		*15 (7)*	*60 (32-84)*
Average for all studies on women with a family history excluding borderline tumours	*3146*		*8*	*25 (3-65)*

Table 4.4 shows the proportion diagnosed at stage I in studies in high risk women. A much larger proportion of tumours in these studies were reported to be borderline tumours, and the proportion of invasive tumours diagnosed at stage I was only 25%. It is difficult to assess to what extent this may be a real difference in women at high risk, or whether it simply reflects the way tumours were classified in these particular studies. Evidence for the latter explanation comes from the fact that one study with a high proportion of borderline tumours[35] was carried out at the same institution and

with some of the same investigators as one of the studies in a general population, which also reported a high proportion of borderline tumours.[62]

4.7 Prevalence of screen detected cancer

Any benefits of screening result from its ability to detect cancer before it would be clinically diagnosed, when it may be more amenable to treatment. The average time period between the detection of cancer at screening, and the time at which it would have been detected clinically in the absence of screening, is known as the lead time. This is determined by both the sensitivity of the test, and the rate of growth of the cancer. The longer the lead time provided by a screening test, the greater its potential to influence the outcome in those screened positive.

The prevalence of screen detected cancer can be used to estimate the lead time.[78] If the number of cases detected at screening is compared with the number which would be expected to present clinically per year, then the length of time it would take to clinically detect the number of cases detected at screening can be used to estimate the lead time. Table 4.3 indicates that the prevalence of screen detected cancer is around 50 per 100, 000. If it is assumed that the screened women would have had an average annual incidence of clinically detected cancer of 40 per 100, 000 (the incidence in England and Wales in women over 40 years[3]), then screening detects around 1.25 years worth of cancer cases. If there is no length bias (i.e. no tendency for screening to preferentially detect slow growing cancers), then this is about double the average lead time. This suggests that ovarian cancer screening may result in a lead time of only 7-8 months. If ovarian cancer has a short natural history, however, this may be sufficient to produce a clinically significant improvement in outcome, although this would also imply that the screening interval would need to be relatively short.

4.8 False positives

Ideally, when assessing the performance of a screening test which has been evaluated in several studies, the sensitivity and specificity obtained in each study should be considered together. However, because so few studies permit a reliable estimate of sensitivity, and these studies use differing tests, thresholds for positive results and study populations, such an analysis would have little value.

The practical significance of the specificity of a test is its relationship with the false positive rate. This is defined as the proportion of all women without the disease (true negatives plus false positives) who are wrongly classified as positive on testing (false positives). Because most of the studies do not have adequate follow-up information, the proportion of true negatives is not known. However, because ovarian cancer is relatively rare in the general population, with an incidence of around 1 in 2500 for the age groups screened, the proportion of women without the disease is close to the total number of women screened. The false positive rate can therefore be approximated by the proportion of screened women who are false positives - i.e., who undergo diagnostic surgery but prove not to have primary ovarian cancer. This is summarised

for studies carried out in women at average risk in table 4.5, and for high risk women in table 4.6.

Table 4.5: False positive rates reported in general population studies

Study	Number screened	Population age and menopausal status	False positive rate: % of all screened women (95% CI)
Ultrasound screening:			
Demidov[69]	11996	18+	2.1 (1.8-2.4)[a]
Campbell[62] (screen 1)	5479	45-78	2.5 (2.1-2.9)
Campbell[62] (screen 2)	4914	45-78	1.8 (1.4-2.2)
Campbell[62] (screen 3)	4201	45-78	1.2 (0.8-1.6)
Tabor[55]	435	46-65	2.1 (0.9-3.9)
Millo[57]	500	45+ or post-menopausal	1.2 (0.5-2.6)[a]
Goswamy[68]	1084	39-78 post-menopausal	1.3 (0.7-2.1)[b]
de Priest[79]	3220	33-90 (mean 60) post-menopausal	1.3 (0.9-1.7)
Ultrasound with CDI			
Kurjak[70]	5013	40-71 (mean 45)	0.7 (0.4-0.9)[a,b]
Vuento[56]	1364	56-61 (mean 59)	0.3 (0.1-0.8)[a,b]
Ultrasound followed by CDI			
Parkes[36]	2953	50-64	0.5 (0.3-0.8)
Ultrasound followed by other secondary tests			
Sato[67]	15282	30+	0.3 (0.2-0.4)[a]
Schincaglia[64]	3541	50-69	0.5 (0.3-0.8)
Holbert[71]	478	30-89 post-menopausal	1.9 (0.9-3.6)
CA125 followed by ultrasound			
Grover[61]	2550	40+ (median 51)	0.3 (01-0.6)
Adonakis[59]	2000	45+ (mean 58)	0.6 (0.3-1.0)
Jacobs[60]	1010	45+ (mean 54) post-menopausal	0.2 (0.02-0.7)
Jacobs[63]	22000	45+ (median 56) post-menopausal	0.1 (0.09-0.2)

a: criteria for positive screening result not fully reported
b: incomplete follow-up: significant numbers of women awaiting further assessment, or significant numbers of screen positive women did not undergo diagnostic intervention
CDI: Colour Doppler imaging

False positive rates varied considerably between studies. There are a number of possible explanations for these differences: random variation; the screening method used; the threshold used to define a positive result; the characteristics of the study population, in particular the menopausal status of the women; and the completeness of

reporting and follow-up of women screened positive. Tables 4.5 and 4.6 show some of these factors.

Studies which used grey-scale ultrasound alone as a screening method have reported higher false positive rates than either those using ultrasound with colour Doppler imaging (CDI) or those using CA125 followed by ultrasound. However, because of the differences outlined above, comparisons of screening methods between studies should be interpreted cautiously. For example, two of the studies using CDI reported significant numbers of women who were still undergoing follow-up and had not been definitively classified as screen positive or negative; this could give a misleadingly low false positive rate.[70,72]

Table 4.6: False positive rates reported in studies on high risk women

Study	Population age and menopausal status (if given)	False positive rate: % of all screened women (95%CI)
Ultrasound screening:		
Andolf[58]	40-70	4.5 (3.2-6.1)[a,b]
Bourne[35]	17-79 (mean 47)	4.9 (3.6-6.4)
Ultrasound with CDI		
Weiner[72]	20-69	2.5 (1.4-4.1)[b]
Ultrasound followed by CDI		
Bourne[35]	17-79 (mean 47)	1.0 (0.4-2.2)
Ultrasound with CA125		
Akulenko[80]	18+	1.3 (0.7-2.2)[a]
Karlan[73]	35+	1.5 (0.7-2.8)[a,b]
Muto[74]	25+	3.9 (2.2-6.4)
Schwartz[75]	30+ (median 42.5)	0.4 (0.0-2.4)[a,b]
Dorum[76]	18+ (mean 43)	8.9 (5.2-14.0)
Belinson[77]	23+ (mean 43)	0.7 (0.2-4.0)[a,b]

a: criteria for positive screening result not fully reported
b: incomplete follow-up: significant numbers of women awaiting further assessment, or significant numbers of screen positive women did not undergo diagnostic intervention

Further evidence that the addition of CDI to ultrasound screening may increase specificity, however, comes from two studies which report separately the proportion of women positive on ultrasound alone compared with the proportion positive after repeat scanning with CDI. [35,36] In one study the proportion of false positives in the first phase of the study using TVS alone was 4.9%, and this reduced to 1.0% after the introduction of CDI.[35] In the second study the proportion reported to be positive on TVS was 3%, and following repeat scanning with CDI the proportion actually referred for surgery was 0.47% (a further 0.3% were referred for surgery outside the screening

protocol).[36] These more direct comparisons have greater validity than comparisons between separate studies.

Similarly, direct comparison between CA125 and ultrasound found that the false positive rate reduced with increasing cut-points of CA125, from 1.1% at 20 U/ml to 0.47% at 35 U/ml, compared with 3.8% with ultrasound alone.[66] This gives strong evidence to support the suggestion from individual studies that CA125 is more specific than ultrasound (see section 4.5). In this study the increased specificity of CA125 was associated with a lower sensitivity compared with ultrasonography.

Table 4.6 indicates that studies on high risk populations tended to have higher false positive rates compared with studies using the same screening method on populations at average risk. This may reflect the generally younger age group, with more pre-menopausal women, included in these studies, or it may reflect the use of a lower threshold for defining a positive result.

4.9 Recall rates

The discussion so far considered as false positives only women referred for diagnostic testing at the end of the screening process but were found not to have ovarian cancer. However, many more women test positive on the initial screen and are recalled for repeat tests than are referred for diagnostic interventions following further assessment. These women will not receive the reassurance of a negative result after attending for screening, and they may experience distress and anxiety while waiting for their follow-up appointments.

Not all the studies reported the number of women recalled for further tests. The recall rate for each study which reported it is given in table 4.7 below. Studies using grey scale ultrasonography as the initial screening test reported recall rates between 5% and 12%. The three studies using ultrasound with CDI had recall rates between 8.5% and 17%, and the studies using CA125 followed by ultrasound reported recall rates between 0.9% and 4%. This provides further evidence of the greater specificity of CA125 based screening. The recall rate therefore varied considerably across the studies, reflecting the different screening methods and thresholds used, and the characteristics of the screened women.

4.10 Positive predictive value of screening tests

If the number of true positives and true negatives are known, then the proportion of those undergoing diagnostic tests who have cancer, the positive predictive value (PPV), can be calculated. The PPV is determined by the test specificity and the prevalence of the disease in a given population. It gives an indication of the relative balance between potential benefits and harms of screening, by measuring the probability that any individual who screens positive, and therefore undergoes diagnostic surgery, does in fact have cancer.

Table 4.7: Summary of results of prospective screening studies

Study	N	population	sensitivity at 1 year (%)	specificity (%)	recall rate (%)	Proportion of false positives among screened women (%) (b/N)	Proportion of screen detected cancers (%) (a/N)	PPV (%) (a/a+b)
Ultrasound screening (transabdominal or transvaginal)								
Goswamy 83[68]	1084	general (post-menopausal)			ns	1.29	0.09	6.7
Millo 89[57]	500	general			5.6	1.20	0	-
Campbell 89[62] (screen 1)	5479	general	100*	96.5	6.1	2.52	0.04	1.0
Campbell 89 (screen 2)	4914	general	100*	98.2	7.0	1.81	0.06	3.3
Campbell 89 (screen 3)	4201	general	100*	98.8	7.4	1.21	0	-
Demidov 90[69]	11 996	general			ns	2.1	0.09	4.2
van Nagell 90[81]**	1000	general			5.4	2.40	0	-
DePriest 93[79]**	3220	general (post-menopausal)			ns	1.27	0.09	6.8
van Nagell 95[65]**	8500	mixed	88	98.7	ns	1.33	0.09	6.6
Tabor 94[55]	435	general			12.4	2.07	0	-
Andolf 86[58]	805	high risk			10.3	4.47	0.37	7.7
Transvaginal ultrasound with colour Doppler imaging								
Kurjak 94[70]	5013	general			8.5	0.68	0.08	10.5
Vuento 95[56]	1364	general	100* 50 at 2 years	99.7	11.7	0.29	0.07	20.0
Weiner 93[72]	600	high risk			16.7	2.50	0.50	16.7
Transvaginal ultrasound followed by colour Doppler as a follow-up test (test method)								
Parkes 94[36]	2953	general	100 50 at 19 months	99.5	ns	0.47	0.03	6.7
Bourne 93[35] (TVS)	1000	high risk	100* 42 at 44 months	95.1	56.8	4.90	0.30	5.8
Bourne 93[35] (TVS/CDI)[1]	601	high risk	100*	99.0	56.8	1.00	0.50	33.3

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Study	N	population	sensitivity at 1 year (%)	specificity (%)	recall rate (%)	Proportion of false positives among screened women (%) (b/N)	Proportion of screen detected cancers (%) (a/N)	PPV (%) (a/a+b)
Ultrasound followed by other follow-up tests (test method)								
Sato 92[67] (tumour markers)	15282	general			5.5	0.3	0.01	4.2
Schincaglia 94[64] (FNAB/C)	3541	general (post-menopausal)	100*	99.5	9.8	0.50	0.06	10.5
Holbert 94[71] (CA125)	478	general (post-menopausal)			6.1	1.88	0.21	10.0
CA125 with ultrasound as a follow-up test (cut-off point)								
Jacobs 88[60] (30 U/ml)	1010	general (post-menopausal)	100*	99.8	3.1	0.20	0.10	33.3
Jacobs 93[63] (30 U/ml)	22000	general (post-menopausal)	79* 58 at 2 years	99.9	1.5	0.14	0.05	26.8
Grover 95[61] (35 U/ml)	2550	general	-	99.7	4.0	0.30	0	-
Adonakis 96[59] (35 U/ml)	2000	general	100	99.4	0.9	0.60	0.10	14.3
Bourne 94[66] (20 U/ml)	1502	high risk	83	98.9	25.2	1.10	0.33	23.8
Bourne 94 (25 U/ml)	1502	high risk	67	99.1	16.1	0.87	0.26	23.5
Bourne 94 (30 U/ml)	1502	high risk	50	99.3	8.5	0.67	0.20	23.1
Bourne 94 (35 U/ml)	1502	high risk	50	99.5	5.5	0.47	0.20	33.3
CA125 with ultrasound								
Akulenko 92[80]	1003	high risk			ns	1.30	0.10	7.1
Karlan 93[73]	597	high risk			19.3	1.51	0.17	10.0
Muto 93[74]	384	high risk			ns	3.90	0	-
Schwartz 95[75]	247	high risk			ns	0.40	0	-
Dorum 96[76]	180	high risk			ns	5.00	8.9	43.8
Belinson 95[77]	137	high risk			ns	0.73	0.73	50.0

*adequate follow-up for 12 months of women screened negative ** some overlap in study subjects

Table 4.7 gives the PPV reported in each of the screening studies. The largest study using ultrasonography alone reported a PPV of 6.7%,[65] whereas the largest study using CA125 achieved a PPV of 27% - just under 3 women on average undergoing unnecessary surgery for every cancer detected.[63] The PPVs reported in individual studies are of limited value, however, because the studies are small and the measures of prevalence of screen detected cancers are imprecise.

Most women undergoing diagnostic surgery are found to have benign pelvic pathology, which may or may not have required treatment if screening had not been undertaken (Appendix 4).

4.11 Pelvic examination as a screening test

Four studies compared pelvic examination (PE) with other screening tests. Three investigated PE compared with CA125,[59-61] and one compared PE with transabdominal ultrasound.[58] Details of these comparisons are given in Appendix 4, table 1g. PE failed to detect the three cancers detected by ultrasound. In the studies comparing PE with CA125, all three cancers detected had either an abnormal or ambiguous examination. The use of pelvic examination as a screening test would have resulted in more false positives than CA125, however. These results, although limited, suggest that pelvic examination does not perform as well as either ultrasound or CA125 as a screening method.

4.12 Adverse effects of screening

The decision whether or not to adopt a screening programme needs to take into account the potential harms of screening. As discussed above (Section 2.1) these include possible over-diagnosis and over-treatment of women with borderline tumours and benign conditions which might not otherwise have caused any morbidity during the woman's lifetime. If operative and psychological morbidity are unacceptably high and the benefits in terms of increased life expectancy are low, then screening will be difficult to justify. These psychological and surgical adverse effects of screening for ovarian cancer are discussed below.

A. Psychological adverse effects of screening: examples from other screening programmes

It is known that false positive results lead to a high level of anxiety in other cancer screening programmes, such as those for cervical and breast cancer.[82,83] This anxiety may be more than simply a transient side-effect: in the case of breast cancer screening a false positive mammogram may cause a significant increase in long term psychological morbidity. Gram et al., for example, reported that after six months the prevalence of anxiety was still higher in those receiving a false positive mammogram, than in a reference group with a negative mammogram.[84] The prevalence of anxiety remained twice as high at 18-months follow-up. Women who received false positive results from mammography screening also report more negative experiences about the screening process such as pain and discomfort.[85] Abnormal test results following Pap tests and

mammograms appear to increase reporting of many other symptoms of psychological distress, such as fear, depression, sleep disturbance, sexual dysfunction and disruption of normal daily activities, though long-term increases in anxiety in false-positives are not consistently reported in all studies of mammography.[86] It might be expected that a further consequence of a false-positive diagnosis is that, as a result of disillusionment with screening, such women would delay in seeking further health investigations. However the opposite effect has also been reported in breast cancer screening, where women with a false-positive diagnosis following mammography subsequently were more likely to practice breast self-examination than those initially screened negative, though this is due to increased anxiety.[87]

Finally, the effects of anxiety are not confined to its effects on the individual; anxiety is likely to be provoked in family members and friends of the woman concerned.

B. Psychological adverse effects of screening for ovarian cancer

Little is known about the reactions to screening of women undergoing screening for ovarian cancer. The background literature search on this subject in MEDLINE, EMBASE, and the psychological abstracts database PSYCHLIT identified only a small number of studies examining this issue (Table 4.8).

True negative diagnosis: One study reported on the psychological impact of a true negative diagnosis of ovarian cancer.[88] This reports the reactions of randomly selected sample of 319 women who had been screened negative (apparent true negatives) in a Swedish programme using abdominal ultrasound. These women with normal results had been "at risk" on the grounds of family history, previous cancer or symptoms, but were not necessarily previously aware of this risk. Anxiety was low on receipt of invitation to screening : a score of 3.5 (range 0-100). The majority of women did not find ultrasound disagreeable (72%) and the majority were satisfied with the amount of information received (92%). 74% felt reassured by the negative result, and the remaining 26% felt "much as before". As regards future screening 88% wished to be examined on a regular basis, 8% were undecided and 4% were against future check-ups, most of who had received hysterectomy and salpingo-oophorectomy. Most women felt the examination to be worthwhile (82%), many saying they now felt reassured and grateful that they had been relieved of their worry about cancer. However this is a highly selected sample, as these are women who both agreed to participate in screening and subsequently agreed to selection for the survey. A greater prevalence of negative attitudes are likely to be found among the non-responders (275/319 - 86% - responded to the survey). It is also well-known that general questions about the acceptability of health care usually do not elicit many negative responses. It has been also been proposed that one consequence of a true negative result may be a "certificate of health " effect, where those screened negative alter their lifestyle in such a way that they believe they can afford to take other risks (e.g. continue to smoke).[89] This has not been examined in the case of ovarian cancer screening.

Table 4.8: Studies reporting psychological effects of screening for ovarian cancer

Study, Country	Sample	Design and data source	Main results
Pernet et al. 1992[91] UK	10 women with family history of ovarian cancer with false positive results following surgery	Qualitative study involving interviews	Women broadly accepting of surgery, but great anxiety before biopsy results made known
Andolf et al., 1990[88] Sweden	319 women "at risk" on grounds of family history, or previous cancer or symptoms	Questionnaire sent to random sample of women screened negative	Anxiety low on receipt of invitation; majority of women satisfied with screening
Wardle et al. 1993[90] UK	302 "high-risk" women	Prospective study comparing anxiety among those with false positive and true negative results	Short-term anxiety associated with a false-positive result but no serious long-term (3 months) psychological effects.
Wardle et al. 1994[92] UK	Self-referred women from general population. Positive on initial scan, subsequently shown to be false positive by scan (n=31) or surgery (n=12)	Prospective study of women with false positive scan, followed up at one year	No significant difference at one year between those originally scanned negative, and the "false positive" group
Wardle et al. 1995[93] UK	358 women interested in ovarian family screening; 379 women who had taken part in screening 1 year previously; 186 controls	Three groups of women were compared with respect to perceived cancer risk and worry about cancer	Worry about cancer highest in those who had attended screening one year previously. Perception of risk not related to participation in screening.
Wolfe 1994[94] UK	1833 women aged 45-74	Questionnaire and information leaflet sent to women identified from FHSA lists to assess acceptability of ovarian/endometrial screening	Majority (76%) willing to be screening, however, those more worried less willing to attend.

Note: Wardle et al. 1993, 1994, 1995 are all part of the same study

False negative diagnosis: A preliminary search for literature on the impact of a false-negative diagnosis has recently been carried out by NHS CRD information staff in order to develop a protocol for a review on the subject. This identified no literature relating to this issue in ovarian cancer screening. Andolf et al. suggest that one result of this diagnosis may be for a patient to delay seeking medical advice in future and ignore symptoms; alternatively the screening programme may have sensitised the patient to symptoms and she may be more likely to seek professional help.[88] Disillusion and resentment are also likely to be a more immediate result. However no data are presented to elucidate these issues.

False positive diagnosis: Evidence of the psychological impact of a false positive diagnosis of ovarian cancer is limited to 3 studies, the first of which reported short-term follow-up results from a group of women at high risk due to family history who

were undergoing either TAS or TVS.[90] 302 women received a scan and participated in the study. Women with an initial positive result were asked to return for rescanning after 6 weeks, and none were found to have cancer at surgery. Questionnaires were mailed after the first scan; 31% of those with a positive scan were worried about cancer, compared to 7% of those with negative scans. Longer term follow-up data were also collected three months after surgery, or after a comparable time period in the other screening groups and in a control group. The anxiety scores (GHQ and HAD) of women with positive results at scanning but negative results at surgery had returned to baseline levels. This suggested that while screening may be associated with distress in the short term it does not persist. However, it should be noted that this is a group of women at increased risk of ovarian cancer, and they may have had a long period to adjust to the possibility of a positive diagnosis at some point in their lives.

There has been one study which has examined the long-term effects of false positive results in a sample of women from the general population, that is, not selected to be at high risk due to their particular family history.[92] In this survey 379 women had referred themselves for screening by ultrasound and 333 received a negative result after the first scan. 46 were referred for a second scan. The authors were therefore able to categorise women into two groups: "scan false positives" (those who received a negative result on the second or third scan, n=31) and those who proceeded to surgery but were found to be disease-free (surgery false positives, n=12). A third group of women with a negative result were also included. All three groups were aged 51 to 53 years (+/- 8 years) and had a mean of 2 to 3 relatives with cancer. There were no statistically significant differences between groups at one year follow-up in either GHQ or State-Trait Anxiety Inventory (STAI) scores. However, both sets of scores appear to have been markedly higher in the "surgery false positive" group, and the sample size is likely to have been too small to have been able to detect a statistically significant difference. The possibility therefore cannot be excluded that long term anxiety is a consequence of a false positive diagnosis, but a larger study would obviously be required. One other notable finding from this study was that anxiety about ovarian cancer was considerable in these women: 29% overall reported themselves "very much worried" about ovarian cancer, and 27% of women who had had surgery were more worried since receiving the result, compared with 10% of "scan positive" and 3% of "scan negative" women.

While the long-term effects (such as shock, distress and fear) of a positive diagnosis of cancer have been demonstrated in studies employing standard anxiety scales, such measures do not give an adequate depiction of the broader impact of a diagnosis on women's quality of life. Qualitative research may provide some of these details and there is one small qualitative study which has reported women's reactions to a false positive diagnosis in a screening programme of asymptomatic women with a family history of ovarian cancer.[91] Ten women aged 27 to 64 years were interviewed at 12 to 21 months after surgery. Psychometric measures were also employed, though as the sample is small and there is no control group these will not be discussed here. The interview showed that 6 of the women had not previously worried about the health of their ovaries, and indeed had been unaware that ovarian cancer runs in families before

they saw the request for volunteers for the study. Despite their results, most women did not feel their participation had been pointless, but were pleased to have taken part in screening and would recommend screening to other women.

Most of the women were very anxious at some time during the scanning procedure, and anxiety was highest between the operation and the results of the biopsy becoming available. Four women were told little about their operation until much later, and two women left hospital without a final biopsy result and spent weeks or months chasing up the results. It is known that delays in notifying results are associated with distress in screening for cervical cancer.[95] In the case of ovarian cancer screening, if some women require repeated retesting before a negative result is notified this will further increase the psychological costs of the programme. Many spouses apparently also found the experience stressful.

The perceived benefit of taking part can be summed up in a quote from one of the participants:

> "I feel a very lucky lady because knowing my family history I am positive that the cyst would have developed into cancer. I have that firmly fixed in my mind".

Finally, one study was found which examined the attitudes of women to screening for ovarian cancer; 76% of women in inner city practices were reported to be willing to be screened using TVS, though the response rate was low.[94]

Summary: For most women the psychological effects of a false positive diagnosis will be short lived and only a small minority may suffer from long-term anxiety. It is easy to assume therefore screening overall has few harmful psychological effects: the majority of women with a false positive result appear to feel grateful that they have been screened, and in the absence of full information about the risks and benefits of screening will probably interpret their eventual negative result as a benefit. However, these are asymptomatic and healthy women without ovarian cancer in whom ovarian cancer is unlikely to have developed and it is therefore doubtful whether the final negative result can really be considered a benefit in these women.

Heightened awareness of ovarian cancer in healthy women who have been screened negative also appears be another consequence of screening.

There is not enough information to determine whether women at high risk and women from the general population differ greatly in their psychological reactions to a false positive diagnosis. Greater anxiety may be provoked in those with a family history as they may feel that cancer is very likely to be diagnosed at surgery. One survey of 242 women with a first-degree relative with ovarian cancer enrolled in the Yale Early Detection Programme found that half reported being increasingly anxious about their own health as they approached the age at which their relative had died.[96] These women may place a different value on having surgery from women in the general population who have been previously concerned about ovarian cancer.

C. Adverse effects associated with diagnostic surgery

There are few published data on the complications associated with oophorectomy. Case series which examine outcomes of laparoscopy tend to include only a small number of oophorectomies, while the larger case series tend to examine oophorectomy carried out at the same time as hysterectomy and do not report separate information for oophorectomy carried out as a single procedure. Moreover, studies which explicitly examine the risks and benefits of oophorectomy tend to examine the long term risks associated with prophylactic oophorectomy, such as osteoporosis and cardiovascular disease, rather than the short term complications associated with the procedure.

However, the literature does provide some limited data (Table 4.9). Only studies with more than 50 women have been included, because smaller studies provide limited information about less frequent complications.

Leetanaporn & Tintara reported on operative morbidity associated with laparoscopic and open salpingo-oophorectomy for benign ovarian cysts in 82 women.[97] Both methods were considered to be safe and effective though little other information on complications is presented. A small comparative study has also assessed laparoscopic oophorectomy in 65 women. Rectus muscle bleeding and haematoma formation were the only complications in this series (3.1%). There were no postoperative complications and no blood transfusions were required.[98]

Possover et al. report their experiences with laparoscopic removal of ovarian tumours in 94 postmenopausal women.[99] Ovarian tumours had been discovered during routine gynaecological examination and/or ultrasound. No intra- or post operative complications were reported and no significant blood loss occurred. Yuen & Rogers reviewed details of a series of 52 women undergoing laparoscopy for ovarian masses.[100] Vaginal ultrasound was performed in all cases before surgery to exclude possible malignancy. Complications occurred in 4 patients (7.7%): one involved laparotomy because of failure to achieve haemostasis, and one involved injury to the inferior epigastric vessels. The other two patients experienced post-operative complications: one required catheterisation for urinary retention and one involved a pelvic haematoma which resolved spontaneously.

A prospective study by Papasakelariou et al. compared the outcome of oophorectomy by laparotomy and laparoscopy in 57 women.[101] Twenty-six (with a mean age of 45 years) underwent laparoscopy and 31 (mean age 48 years) underwent laparotomy. Half of the women in each surgical group had adnexal masses. No serious complications occurred in the laparoscopy group; none of the women were readmitted with complications. Two serious complications (6.5%). - one bowel injury and one bladder injury - occurred in the laparotomy group. These were repaired intra-operatively with no long term sequelae. In addition, one woman received a blood transfusion, and two had post-operative fever.

Table 4.9: Studies reporting complications of laparoscopic examination of ovarian masses

Study, Country	Procedure and sample size	Design and data source	Results
Leetanporn & Tintara (1996) [97] Japan	82 women undergoing either laparoscopic (LSO) or open salpingo-oophorectomy (OSO) for benign ovarian cysts	Comparative study comparing LSO cases with historical OSO controls	LSO is safe and effective alternative to OSO
Minelli (1996) [104] Italy	Laparoscopic removal of ovarian cysts in 920 women	Retrospective analysis of authors own data	13 converted to laparotomy; 5 severe intra or post-operative complications (0.5%)
Papasakelariou et al. (1995) [101] USA	Oophorectomy by laparoscopic or laparotomy in 57 women with pelvic pain, adnexal masses or endometriosis	Prospective analysis of data collected during 1992. Data collected from logs in the operating room, and review of medical records	No serious complications in laparoscopy group. No laparoscopies converted to laparotomies.
Canis et al. (1994) [105] France	Laparoscopy for adnexal masses in 757 women aged 36+/- 13 years	Retrospective review of data on all patients between 1980 and 1991	8 complications (1.1%) , three involving spillage of cyst contents
Possover et al. (1994) [99]	Laparoscopy in 94 post menopausal women with ovarian tumours (mean age 61 years).	Retrospective data from one medical centre between 1992-1993	No peri- or post-operative complications and no significant blood loss
Yuen & Rogers, (1994) [106] Hong Kong	52 women undergoing laparoscopy for ovarian masses (median age 35 years). Presenting complaints included pelvic pain (19 patients), infertility (4), abnormal uterine bleeding (7) and asymptomatic pelvic mass detected during routine check-up (23).	Data on 52 consecutive patients were reviewed	Post-operative pain reported to be "minimal". Overall complication rate was 7.7%, and included need for catheterisation, haematoma, epigastric vessel injury
Reich et al. (1993) [102] USA	Laparoscopic oophorectomy in 312 women undergoing unilateral or bilateral oophorectomy for symptoms including pain and/or adnexal mass	Retrospective analysis of physician and hospital data from 1982-1990	Intra-operative and/or postoperative complications reported in 12 (3.8%) women. Blood loss >300 ml in 2 women (0.6%). Length of hospitalisation <24 hrs in 78% of women.
Daniell et al. (1992) [98] USA	Laparoscopic oophorectomy by ligature, bipolar coagulation or stapling in 65 patients aged 16-57. Indications included pain, ovarian endometriosis, and recurrent benign ovarian cysts	Comparative study of three methods of oophorectomy. Data collected retrospectively from hospital records from 1989-1991	Rectus muscle bleeding and haematoma formation occurred in 2 patients (3.1%)
Mage et al. (1991) [103] France	481 patients with suspected benign ovarian cyst undergoing diagnostic laparoscopy	Retrospective analysis of hospital data (1981-1988)	3/420 patients (0.7%) undergoing intraperitoneal or transparietal cystectomy developed a complication -no details given

One case series was found which specifically reported information on 312 laparoscopic oophorectomies performed over an eight year period on women of median age 39 years.[102] Intraoperative or postoperative complications occurred in 12 women (3.8%). These included two bowel injuries. One of these women also developed adult respiratory distress syndrome. Bleeding from the anterior abdominal wall at the secondary puncture site occurred in one woman. Post-operative complications included post-operative voiding difficulty requiring catheterisation, two urinary tract infections, one case of hydronephrosis requiring a stent and one ileus which resolved spontaneously. Blood loss greater than 300ml occurred in two women (0.6%).

Three other relatively large studies report on the outcomes of laparoscopic investigation for ovarian abnormalities and these also suggest that the incidence of complications (such as haemorrhaging and post-operative inflammation) is in the range 0.5% to 1%. The first of these is a large case series reporting the outcomes of diagnostic laparoscopy for suspected benign ovarian cysts in 481 women between 1981 and 1988.[103] Laparotomy was carried out in 61 women (mean age 34 years), where anatomical conditions made laparoscopy difficult, or in cases of suspected malignancy. In the 420 women undergoing laparoscopy with either intraperitoneal cystectomy or transparietal cystectomy there were 3 unspecified complications (0.7%). The second study reported on the laparoscopic management of ovarian cysts in 920 women.[104] Five severe complications occurred in total, either intra- or post-operatively (0.5%). These included one ovarian abscess leading to subsequent laparoscopic adnexiectomy, one inflammation of the abdominal wall, one case of uncontrollable intra-operative haemorrhaging, one case of post-operative haemorrhaging, and one case of post-operative acute abdomen. No other information is provided regarding the selection or characteristics of the cases reported in this series. Finally, Canis et al. studied the immediate and long-term consequences of laparoscopic diagnosis of adnexal cystic masses.[105] Long-term follow-up used data obtained either clinically or by mailed questionnaire. 757 women aged around 36 years were investigated and 8 complications were attributed to the investigative procedure (1%), three of these being spillage of cyst contents.

The prospective screening studies are another potential source of information on the adverse effects of surgery and the adverse psychological effects of screening. However, only one study has reported this information.[74] This reports one small bowel perforation requiring segmental resection, with no other intraoperative or post-operative complications, out of 15 undergoing surgery (6.7%).

These small case series examining outcomes of oophorectomy or of management of ovarian and related abnormalities therefore tend to suggest that complications are rare, and that when they occur are minor. However these studies are too small to provide a reliable estimate of the incidence of rare events. No large (i.e., >1000) case series were found.

An estimate of the risks associated with laparoscopic management of suspected ovarian malignancy can however be made. On the basis of the larger case-series,

0.5%-1% of women may experience complications associated with laparoscopic oophorectomy. These include bleeding and post-operative infection but may also involve more serious complications such as bowel injury. However this figure should be interpreted with caution as the studies cited here may differ from procedures likely to be carried out as part of a screening program. There are likely to be differences in age and casemix and in particular the actual procedure will be different, as most of the screening studies identified in this review were open procedures rather than laparotomies. Moreover, these studies do not provide estimates of the risk of mortality and do not accurately represent the true morbidity associated with diagnostic surgery, rather than just the rate of surgical complications.

4.13 Costs of screening

The search strategy identified one model of the relative cost-effectiveness of different screening strategies. This is discussed in section 6. In addition, several articles report data on charges in the United States for various components of screening. Charges for transvaginal ultrasound scans vary between $150 and $275,[107,108] while costs for CA125 testing vary between $45 and $61. [77,108] The charge for a laparoscopy is reported as $3, 000, indicating that a critical component of the total costs of screening will be the proportion of women referred for surgery.[107] One published report gives the actual costs, rather than charges, over time incurred in establishing and running an ultrasound based screening programme.[37] This gives a marginal cost for each ultrasound scan of only $25 once the programme was running at full capacity, and illustrates that the actual costs of screening may bear little resemblance to putative costs based on charges. In this study, the majority of costs incurred for each case of ovarian cancer detected resulted from the diagnostic procedures undertaken.

It seems reasonable to assume that the cost of screening each woman with ultrasound will be higher than the cost for CA125 followed by ultrasound. Ultrasound screening requires investment in equipment and trained personnel, and requires centralised facilities for women to attend for screening. In contrast, collecting blood for CA125 is a simple procedure which can be carried out in any location, with samples transported for bulk analysis. However, the total cost of these screening options also depends on the numbers of women recalled for further assessments and for diagnostic procedures. A recent model comparing annual TVS to annual CA125 followed by TVS in those with elevated or rising levels, and using charges to estimate costs, found that the cost per life year saved was lower for the CA125 strategy.[107]

5 RESEARCH IN PROGRESS

5.1 Randomised controlled trials of ovarian cancer screening

Three RCTs are in progress, investigating the effect of screening for ovarian cancer on mortality from the disease in women from the general population. Two of the trials are being co-ordinated in the UK: the Barts trial is recruiting women within the UK,[109] and the ERTOCS trial is a multicentre trial open to participating centres throughout Europe.[110] The third trial is being carried out in the United States; the PLCO trial co-ordinated by the National Institutes of Health (NIH) investigating screening for prostate, lung and colorectal cancer, as well as ovarian cancer.[111]

Protocols for each of these trials have been supplied by the investigators and the key features are summarised in table 5.1. These protocols are subject to on-going review and the details contained in the tables are those most recently made available.

A trial of screening requires recruitment of healthy women who have not sought treatment. In this respect it is unlike a trial assessing treatment options, where the trial is ethically justified if there is uncertainty about the relative merits of different treatments. For a trial of preventive measures, there is a particular duty to ensure that the level of risk to which healthy volunteers are be exposed is acceptable relative to the potential benefits, and that the volunteers are fully informed.

The following discussion appraises the design of these trials and assesses the information they will provide if successfully completed.

a) Screening algorithms being evaluated

The Barts trial is investigating the use of annual screening with CA125 followed by ultrasound as a screening strategy. The protocol differs from that used previously by these investigators,[63] in that decisions to recall for repeat CA125 level or scan will be based on the woman's risk of ovarian cancer, calculated on the basis of age and the level and rate of change of CA125. In some circumstances women will be referred on the basis of CA125 measurements in the presence of a normal scan. Women with equivocal results will be recalled for further testing, though to avoid repeated recalls a maximum of five recalls will be allowed for repeat investigations using ultrasound. A retrospective analysis of data from a previous screening study found that this algorithm resulted in a false positive rate of 0.3%.[112] The cut-off point for recall for repeat testing is relatively low, at 15 U/ml, and this means that a large proportion of women, perhaps more than 25%, will be recalled for repeat testing.

The ERTOCS trial uses transvaginal ultrasound as a screening test. The algorithm for determining a positive result is complex, but essentially all ovarian abnormalities apart from small simple cysts will result in recall for further assessment. A maximum of three scans including the initial scan is carried out before a definitive decision on referral is made.

Table 5.1: on-going RCTs of screening

Study	Barts[109]	ERTOCS[110]	NIH PLCO[111]
Setting	UK	UK/Europe	US
Start date	1995?	1995?	1993?
Screening protocol	CA125 followed by ultrasound in those testing positive - calculated on basis of age, level and rate of change of CA125 Annual screenings for 6 years	TVS at either 18 or 36 month intervals Referred for repeat scan if ovarian volume >=3 multiple of the median (post-menopausal) or >=4 MoMs (pre-menopausal), or if cyst present, unless simple unilocular cyst with regular outline and <50mm dia.	TVS and CA125 and pelvic examination. Positive results not strictly defined, but any positive/suspicious result leads to referral to patients' own physician Annual screenings for 4 years
Study population	Post-menopausal women aged over 50	50-64 years	Women aged between 60 and 74
Recruitment	Volunteers: recruited via press, through occ. health depts and by invitation in participating general practices	Women selected either from a population registry or invited when attending for breast cancer screening	Volunteers: recruited through press
Target number of subjects	60, 000 in each arm	30, 000 in each intervention arm, 60, 000 in control group	37, 000 in each arm
Follow-up - method and length	Cancer registrations Postal questionnaire at 4 and 7 years	Cancer registrations/ death notifications Length of follow-up not given	Annual postal questionnaire Death registrations Follow-up: 10 years
Estimated number of O.C. deaths in unscreened group	111 over 6 years		not given
Stated power	80% power to detect 30% reduction in mortality at 5% significance level	78% power to detect one third reduction in mortality at 5% significance level	77% power to detect 30% reduction in mortality at 5% significance level
Expected date of completion	7 years follow-up	10 year follow-up?	10 year follow-up
Uptake/acceptability assessed?	no	Yes	no
Evaluation of costs?	If funding permits	Planned	no
Evaluation of harms?	Will measure surgical intervention rates in both arms Evaluation of psychological effects if funding permits	Data on surgical complications to be recorded in those referred for diagnosis.	State that morbid events associated with screening or diagnosis will be recorded
Comments	Preliminary results of stage distribution in screen detected cancers available at 4 years	Stage distribution in screened and control groups obtained by 4 years. Serum collected from screened women to enable retrospective analysis of tumour markers Colour Doppler imaging also performed at repeat screening for retrospective analysis	Should allow comparison between the 3 methods. However the looseness of definition of positive result means the false positive rate is likely to be high

A pilot study using a similar algorithm reported 3% of women with persistent abnormalities on ultrasound screening.[36] In this pilot phase of the study, colour Doppler was used as a secondary test and a false positive rate of 0.5% for surgical referral was reported; however, subsequently the use of colour Doppler as part of the screening algorithm has been dropped because this reduction in false positive rate was not maintained.

The PLCO trial is investigating annual CA125, pelvic examination and transvaginal ultrasound as screening tests. These are carried out independently and in a blinded fashion on each woman. The study protocol does not give specific definitions of abnormal results but states that women with abnormal or equivocal results will be referred back to their own doctor for follow-up.

This protocol is similar to the screening protocols which have been used in screening high risk women. However, due to the looseness of the definitions of abnormal screening results, the lack of a protocol for further management, and the lack of repeat screening to rule out transient changes, the proportion of false positives is likely to be higher than that reported in prospective screening studies.

In the populations being screened in these studies, the expected incidence of ovarian cancer is 40 per 100, 000 per year, and based on published studies it seems unlikely that the prevalence of cancer detected on screening will exceed double this, or 0.08%. A false positive rate of 1% will therefore result in about 12 diagnostic operations for each cancer detected. The Barts study may achieve a higher PPV, and the ERTOCS and PLCO, a lower PPV. It is notable that one of the centres participating in the ERTOCS study has stopped recruiting after 13, 000 women were randomised, due to the unexpectedly large number of complications in women undergoing surgery (Tabor, personal communication).

The ERTOCS trial has two intervention arms, one screened at 18 months and one screened at 3 years. This allows investigation of the effect of screening interval on the benefits, harms and costs of screening.

b. Sample size and power

The two UK based trials aim to recruit 120, 000 women each to randomisation. This sample size is calculated to have 80% power to detect a 33% reduction in ovarian cancer mortality in the screened group, at a significance level of 5%. This is based on a total of around 110 ovarian cancer deaths in the 60, 000 controls over 4 years.

The PLCO trial aims to recruit a total of 74, 000 women to randomisation. It is calculated that this will give a 77% power to detect a 30% reduction in mortality after 10 years follow-up, at the 5% significance level. However, screening for ovarian cancer is already becoming widespread in the US, and therefore contamination may be a problem for this trial, reducing its power.

c. Population selection

Both the Barts and the PLCO trials are recruiting volunteers from a range of sources, but principally from women who respond to publicity disseminated through a variety of channels. Neither of these trials is designed to allow a calculation of the uptake of screening in a randomly selected general population sample. Selection bias may result in a healthier than average group of women participating in the trial, which might reduce the prevalence of cancers and therefore the power of the study.

In the ERTOCS trial, recruitment in the UK is by invitation to women attending breast screening, allowing uptake rates to be measured. These women may not be representative of a general population invited for screening, since they have already chosen to participate in a screening programme. Participating centres in Europe which sample women from a population register may give a more accurate estimate of the effect of selection bias and the uptake of screening.

d. Outcome measures: assessment of morbidity and costs, assessment of mortality

All three trials measure mortality from ovarian cancer as a final endpoint. The ERTOCS study relies on reporting of cancers via routine data systems such as cancer registries and death certificates for ascertainment in the control group, whereas the other trials also use postal questionnaire follow-up. There may therefore be differences in case ascertainment between the trials.

The Barts trial sends questionnaires to both screened and control groups, enabling investigation of the effect of screening on the number of gynaecological procedures carried out. This may provide information relevant to the question of the natural history of screen detected benign ovarian conditions.

All trials will record the nature of surgical procedures undertaken in the screened group and any complications arising, thus enabling quantification of the morbidity in false positives arising due to screening. However, this will be restricted to description of the prevalence of complication rates, rather than a fuller measurement of morbidity and quality of life. The two UK based trials plan to incorporate an economic analysis of screening. The Barts study however has not yet developed a protocol for this aspect of the trial.

The Barts trial also intends to incorporate investigation of the psychological impact of screening, but again a protocol has not yet been developed. The other two trials have no plans to investigate this aspect of screening.

e. Scope for assessment of new screening strategies

All three trials will establish a serum bank with stored samples from screened women. This will facilitate the investigation of the value of newly identified markers, or novel ways of combining or interpreting markers, in a large cohort of women with good

follow-up data on the incidence of ovarian cancer. The ERTOCS and PLCO studies will have ultrasound data on all screened participants and will therefore be able to investigate the effect of using various serum markers either in comparison with, or combined with, ultrasound screening.

The ERTOCS trial is also recording information from colour Doppler imaging on women who have an abnormal ultrasound scan. This should enable a fuller assessment of the value of colour Doppler as a secondary test to be made. The information recorded on the ultrasound findings will also allow correlation with the risk of malignancy. This could help in the development of more specific criteria for diagnostic intervention.

f) Conclusions

These three trials should all provide reliable information concerning the effect of screening on ovarian cancer mortality and incidence. They will also build up valuable data sources for the development of improved screening methods.

The main weaknesses of these studies are the absence of an assessment of some of the 'softer' outcomes of screening, both in terms of the morbidity experienced by both true and false positives, and in the psychological impact of screening. This is particularly important in view of the large proportion of women who are likely to be recalled under the proposed protocols, and the relatively poor information so far published concerning the effects of diagnostic surgery.

Another important issue is the measurement of the cost-effectiveness of screening. Ideally, the costs and consequences of screening should be measured in the trials in such a way as to permit comparison of the cost-effectiveness of the very different screening strategies being evaluated. This would require increased collaboration between the research teams.

These studies all began around 1994-5, and results relating to mortality effects may not be available until around 2003. However, intermediate outcomes of interest such as the false positive rate and the morbidity in false positives could be available much sooner than this if the investigators wished to publish them.

5.2 Studies on screening in women with a family history

There are no RCTs currently in progress in the high risk population. However, if the natural history of ovarian cancer is similar in this group, the results of the RCTs carried out in the general population could be used to model the cost-effectiveness of screening in a group with a higher prevalence of the disease.

Screening is currently being offered as a service in the UK to some women with a strong family history of ovarian and other relevant cancers. There is a reluctance to establish RCTs in this group because of their high risk of developing ovarian cancer; the average lifetime risk of developing ovarian cancer for women with two affected

close relatives is about 15%, which is about one and a half times the average lifetime risk of developing breast cancer.

The UKCCCR has recently established a prospective uncontrolled screening study for women with a family history of ovarian cancer.[113] The eligibility criteria for the study require a history of more than one close affected relative, such that this group has an average lifetime risk of developing ovarian cancer of at least 15%. This study has no comparison group and therefore cannot provide information about the effectiveness of screening. Like the prospective screening studies whose results have been published, it can only provide information about the performance of the screening test and the risks of screening.

The screening protocol proposed for use in this study includes annual CA125 and transvaginal ultrasonography. This protocol has been selected to maximise sensitivity at the expense of specificity and is not directly comparable with the protocols being evaluated in the UK based RCTs. A high proportion of women may be recalled for repeat tests - 5% estimated following ultrasonography, and perhaps 15% for repeat venepuncture.[66] The main research objective of this study is to collect data to develop a model to determine an individual's risk of ovarian cancer. It is hoped that the use of this model in a screening algorithm might improve sensitivity and specificity.

The incidence of ovarian cancer will be measured through cancer registry data, giving information about the sensitivity of screening and the risk of developing ovarian cancer in this group. There is no provision in the protocol to collect data on operative morbidity of false positives, nor on the psychological impact of screening in this group of women. The study therefore concentrates on attempting to devise an improved screening method, while paying less attention to the opportunities afforded by this study design to investigate the consequences of screening.

This study may have two unplanned consequences. Firstly, it may improve the quality of screening already being offered to women at high risk in participating centres, by providing a clear screening protocol and quality control measures. Secondly, the study seeks to actively recruit women from the general public by publicity. Recruiting to a non-randomised study in this way may give the erroneous impression that screening has been proven to be safe and effective. It will also increase awareness and anxiety about ovarian cancer among women with a family history, most of whom will not fulfil the criteria for entry into the study. This is likely to increase demand for screening among a far larger group of women than those at whom the study is aimed.

5.3 Unpublished studies

Authors of all prospective studies included in the review were contacted to establish whether they had further unpublished data relating to their screening studies. One group of investigators is preparing for publication data relating to three annual incident screens in 11, 000 women randomised to CA125 screening (Jacobs, personal

communication). This data will provide information relating to the outcome of repeated screening rounds based on CA125, and will also provide comparison with the control group who received one initial screen.

There are further unpublished data relating to repeated screenings with transvaginal sonography. A cohort of high risk women have undergone three screening rounds, but published data relate only to the initial screen.[35] Due to lack of funding the data relating to incident screenings are likely to remain unpublished (Bourne, personal communication). The largest TVS screening study in the US has also undertaken several screening rounds in its participants. Unfortunately the published data have not reported the results of each round separately.[65]

6 DISCUSSION

6.1 Limitations of the published research evidence and the review methods

The published research evidence gives only limited information about the potential impact of ovarian cancer screening. Some of these limitations result from the study designs used, and some from the quality of the conduct and reporting of the studies. Uncontrolled studies of screening cannot give reliable information about the effectiveness of screening - this requires randomised trials comparing mortality in screened and unscreened populations.[34] The main role of such studies is therefore in assessing whether screening test performance is adequate to justify the establishment of an RCT, and to help decide which screening methods should be investigated in such trials. Such studies can also be used to assess the adverse effects and the costs of screening.

To investigate these issues reliably, prospective uncontrolled studies need to be designed robustly with a clear research aim. A study aiming to evaluate the performance of screening tests should define the screening protocol before the study commences, and report data relating to all study subjects, including those lost to follow-up. If sensitivity is to be estimated, women must be followed up following a negative test result, and the study must be large enough to expect to detect a substantial number of ovarian cancers. Many published studies did not meet these standards.

The proportion of false positives, and hence an estimate of test specificity, can be more readily estimated from this type of study. However, comparison of test specificities in different studies, without also considering sensitivity gives limited information because the two parameters are interdependent. Specificity estimates can also be affected by the completeness of follow-up of women recalled for further tests - the proportion of false positives may be underestimated if large numbers of women are still awaiting definitive results from screening, or if some women failed to attend. Not all studies indicated the completeness of the information reported, and there was little detail reported on the actual procedures performed on women screened positive, and the outcomes or complications associated with these procedures.

Uncontrolled studies can also be useful in comparing the relative performance of different screening tests and algorithms, in order to define appropriate tests for use in a trial. The most valid way of making such a comparison is to perform each screening test on the same women, with observers blinded to the results. However, there is only one such comparison published, between CA125 and ultrasound.[35] This means that there is little reliable evidence on which to base comparisons of different screening tests. A further area which has been underreported is the effect of repeated screening rounds; data from each screening round should be reported separately to investigate

the effect of repeated screening on detection rates and false positive rates. Only one study has so far published such data.[62]

Most of these studies were carried out on volunteers, and the method of recruitment was often not fully defined. This means that estimates of uptake cannot be made, and no assessment of the likely impact of selection bias can be made. It is therefore difficult to assess the degree to which selection bias may have influenced the findings, and to judge the relevance of the studies to offering screening in an unselected population.

Many studies have investigated test performance in women undergoing surgery for suspected ovarian masses. However, such studies are not directly applicable to the screening situation because many of the women have clinically detectable ovarian abnormalities, and the estimates of sensitivity and specificity obtained cannot therefore be directly applied to the detection of pre-clinical ovarian cancer in asymptomatic women. Studies of this type were therefore not systematically reviewed, and fairly restrictive inclusion criteria were set to increase the validity of the findings of the review.

Obtaining evidence about the potential complications of surgery in false positives necessitated the use of a specific search strategy, because of the lack of information reported in the published screening studies. It was not intended to identify all potentially relevant studies, but simply to identify case series of surgery potentially relevant to the diagnostic surgery undertaken as part of the screening process. The case mix and the nature of the surgical intervention may not be directly comparable to that observed in a screening study, and the resulting estimates of complication rates are clearly less reliable than if estimates taken directly from a screening study had been available.

6.2 Summary of research evidence

Available evidence suggests that screening with ultrasound, with or without colour Doppler imaging, or with CA125 followed by ultrasound, can detect ovarian cancer in asymptomatic women at an earlier stage than in an unscreened population (resulting in approximately 50-75% of cancers diagnosed at stage I). Screening with ultrasound (transvaginally) appears to have a higher sensitivity, but a lower specificity, than CA125 followed by ultrasound. Colour Doppler imaging added to grey-scale ultrasonography may increase specificity but the consequences for sensitivity are unknown.

Sensitivity of ultrasound screening, defined as the proportion of cancers arising in one year which are detected on screening, appears to be close to 100%, but this is based on limited information. Sensitivity of CA125 followed by ultrasound at 1 year appears to be around 80% (95% CI 49-95%). The prevalence of screen detected cancer and the proportion of cancers detected at stage I are consistent with some improvement in stage at diagnosis compared with an unscreened population, but the precision of these estimates is low, and the clinical significance in terms of the potential impact on

mortality from ovarian cancer is unknown. There is little information on the impact of repeated screening or on the optimum interval between screenings.

Some women may have tumours of borderline malignancy diagnosed at screening which may not have been clinically detected in their lifetime, resulting in potentially unnecessary intervention and treatment. This may be more likely to occur with ultrasound screening. The available information suggests that the overall proportion of borderline tumours reported in screening studies is consistent with that expected in the population as a whole;[5] however these tumours have tended to be concentrated in particular studies suggesting that there may be inconsistencies in the way these tumours are classified and reported. The extent of possible overdiagnosis can only be assessed in randomised trials which can compare the incidence of ovarian cancer in screened and unscreened populations.

The proportion of women screened who were false positives ranges from around 0.1 - 0.6% for screening with CA125 followed by ultrasound, to 1.2-2.5% for grey-scale ultrasound screening alone. Most women undergoing diagnostic surgery who are found not to have cancer, are found to have a benign ovarian or gynaecological condition. The potential benefits of surgical intervention in this situation are unknown. The risks of surgery include a small chance of death, and also the risk of significant complications such as bowel or bladder damage, infection or excessive bleeding. The risks are difficult to quantify but may be around 0.5-1% of those undergoing diagnostic surgery. Complication rates however give only a limited picture of the adverse effects experienced by women who are screened positive but are found not to have cancer . In addition to these risks, a much larger proportion of women who do not have cancer (perhaps 3-12% of all screened women) will be recalled after the initial screening test for further assessment, and these women may experience distress and anxiety while awaiting the result of these tests.

A definitive answer to whether screening can improve the outcome for women with ovarian cancer requires a RCT of screening. On-going RCTs, if successfully completed, will not report their results for at least 5 years. Such trials, as well as quantifying any benefits and harms of screening, could also provide information concerning the relative cost-effectiveness of different screening methods and screening intervals.

In the absence of direct evidence about screening from RCTs, models of the potential impact of screening can be constructed which may help in making judgements about screening. The reliability of these models depends on the accuracy of the assumptions which are used in place of empirical evidence. Nevertheless, they may be helpful in assessing the likely health gain which ovarian cancer screening might achieve, and therefore in judging the relative priority of NHS support for further research in this area.

6.3 Modelling the impact of ovarian cancer screening

A number of authors have attempted to model the impact of ovarian cancer screening.[36,107,114-116] Details of the methods and findings of these modelling studies are given in appendix 5.

The simplest model estimates the percentage reduction in ovarian cancer mortality 5 years after screening, by combining estimates of the proportion of cancers detected at stage I in screened women with currently observed stage-specific survival rates.[36] Table 6.1 shows the percentage mortality reduction predicted by this model over a range of different proportions of cancers diagnosed at stage I.

Table 6.1: Effect of proportion of ovarian cancers diagnosed at stage I on estimated mortality reduction[36]

Proportion of stage I cancers in screened population	Expected reduction in mortality compared with unscreened population (%)*
34	0
50	15
80	43
100	61

* assumes 34% present at stage I in the absence of screening, and 5 year survival of 75% at stage I and 16% at all other stages

This highly simplified model demonstrates that a maximum 61% reduction in mortality could, theoretically, be achieved if all women with ovarian cancer are diagnosed at stage I and the current 5 year survival rate applies. However this theoretical reduction is extremely unlikely to be achievable in practice as it assumes no cases are missed, and that survival rates currently observed apply to screened stage I cancers. It also assumes very frequent screening. If 75% of cancers are diagnosed at stage I, (based on published screening studies; Table 4.3) this model predicts a mortality reduction could range from 0% and 61% at 5 years, but is most consistent with a reduction of 40%.

The authors calculate the cost per life saved by ovarian cancer screening to be around twice as much as that for breast cancer screening. This is based on a number of fairly optimistic assumptions: 43% reduction in mortality in screened women, equivalent to 80% diagnosed at stage I; a screening interval of 3 years; and the same cost per screen as for breast cancer. Under these assumptions, for every 10 000 women screened, there would be 1.6 extra 5 year survivors per year.

Similar methods using observational survival data from the United States suggest that screening might result in a 50% reduction in ovarian cancer mortality, equivalent to 85% of cancers in screened women diagnosed at stage I.[116] For annual screening, this implies 1.7 additional five-year survivors for every 6000 screening tests performed.

A decision analysis model based on a once only screen and taking account of the adverse effects of laparotomy, calculated the average increase in life expectancy in a screened population to be around three-quarters of a day for women screened at age 65.[114] These authors calculate that breast screening would achieve around twice as much gain as ovarian cancer screening. The simple stage shift model (which includes no allowance for adverse effects) assumed that each extra 5 year survivor would gain an extra 19.3 years of life.[36] This is equivalent to just over one day of life gained for each women screened, the same order of magnitude as that estimated by this decision analysis model.

More complex models use computer simulation to reflect the dynamic nature of the growth of cancers and their likelihood of detection over time. One such model, which used clinicians' estimates to model the natural history of ovarian cancer, predicts an average of 3.4 years gained for every case of ovarian cancer (screen detected and clinically detected) for CA125 screening.[115] This is rather lower than that estimated by the simple stage shift model, which suggests around 7.7 years gained per ovarian cancer case.

Building on this model, using the same estimates of the natural history of ovarian cancer, Urban et al have compared the relative cost-effectiveness of ultrasound (TVS) screening and CA125 screening followed by TVS.[107] The model resulted in 66% of cancers diagnosed at stage I for the TVS strategy, and 51% diagnosed at stage I for the CA125/TVS strategy, similar to the average proportions in published screening studies (table 4.3). The number of life years saved according to this model, was equivalent to only about one year for each case of ovarian cancer in the population. This model estimates that for annual screening, the CA125 strategy saves nearly two thirds of the number of life-years compared with the TVS strategy at about one third the cost. CA125 retained its cost-effectiveness advantage across a wide range of sensitivity analyses. The authors did not consider the effect of less frequent TVS screening, as is being investigated in one of the on-going RCTs.

The limitation of all these models is that they must rely on assumptions of treatment effectiveness based on currently observed survival rates at different disease stages, and may therefore over or even under-estimate the likely benefit. They cannot replace RCTs as a means of establishing whether or not earlier detection can improve outcome. Furthermore, the published models have in general been less useful for assessing the size and distribution of any adverse effects; these are either ignored, or added together with benefits to produce a figure for the 'net benefit', which does not allow consideration of the distribution of benefits and harms.

6.4 Potential benefits and harms

In this section the potential balance between benefits and harms which may result from screening for ovarian cancer is considered. In the absence of evidence concerning benefits, a level of benefit will be assumed which is consistent with the more encouraging results from published studies. If early detection and treatment is effective, benefits and harms could be experienced in terms of survival and quality of

life. In the rest of this section, potential benefits are only discussed with respect to length of life or mortality.

The smallest effect on ovarian cancer mortality that the trials currently in progress can be confident of detecting is a 30% reduction. The maximum likely achievable reduction is 60%, equivalent to 100% of cancers being diagnosed at stage I at current survival rates.

Table 6.2 shows the absolute reduction in mortality rate corresponding to this range of relative mortality reduction assuming that screening is offered to women between the ages of 50 and 64 (who have a higher incidence of ovarian cancer than younger women but still have a reasonable life expectancy) and the mortality reduction occurs 5 years later. This shows that the number of extra five year survivors gained per 100, 000 women screened per year is likely to be quite small, because the number of deaths due to ovarian cancer is relatively low (about one third that of breast cancer in this age group). The total number of extra survivors depends on the period over which screening is offered and the duration of any effect on mortality. The number of life years gained is difficult to estimate because the proportion of extra 5 year survivors who are 'cured' in the long term is unknown.

Table 6.2: Illustration of mortality reduction per year for a given percentage reduction in mortality

	% reduction in mortality from ovarian cancer			
	30	**40**	**50**	**60**
Absolute reduction in mortality in screened women (number of extra survivors at 5 years per 100,000 per year*)	11	15	18	22

*Based on 1994 mortality rate in England and Wales in women aged between 55 and 69 of 36.5 per 100 000

If we now assume that ovarian cancer screening results in a 40% reduction in mortality, this is equivalent to 15 extra survivors at 5 years per 100,000 women screened per year. This is equivalent, at current survival rates, to nearly 80% of cancers being diagnosed at stage I, and is consistent with the results reported from the more encouraging prospective screening studies (table 4.3). It is also more favourable than the stage shift resulting from the most sophisticated screening model,[107] and might therefore be considered a relatively optimistic assumption.

Table 6.3 illustrates the outcomes which might result in a hypothetical cohort of 10,000 women who have an average annual incidence of ovarian cancer of 40 per 100,000 - the approximate incidence in the UK for women aged 50-64. The table shows potential annual outcomes of screening in the 'steady state'. Two illustrative scenarios are given; the 'CA125 scenario' which assumes annual screening with 3% of women recalled and 0.2% of women undergoing surgery for conditions other than

ovarian cancer, and the 'TVS scenario' which assumes bi-annual screening with 7% of women recalled and 1.3% of false positives at diagnostic surgery. These assumptions are consistent with the results reported in the more favourable prospective screening studies, so may be optimistic. It is assumed that both of these strategies result in the same benefit - 40% reduction in ovarian cancer mortality.

Table 6.3: Annual outcomes of screening in a hypothetical cohort of 10,000 women assuming 40% mortality reduction and annual incidence of 1 in 2500 for ovarian cancer (see text for discussion of assumptions)

	'CA125 scenario'	'TVS scenario'
Number of women participating in screening programme	10,000	10,000
Screening interval	Annual	Every two years
Number of screening tests carried out per year	10,000	5,000
Number of women recalled for further assessment per year	300 (3% of screens)	350 (7% of screens)
Number of women undergoing surgery per year who do not have primary ovarian cancer	20 (0.2% of screens)	65 (1.3% of screens)
Maximum number of cancers detected on screening per year (if 100% sensitivity)	4	4
Number of additional 5 year survivors per year	1.5	1.5
Predictive value of recall (if 100% sensitivity)	1.3%	1.1%
Predictive value of diagnostic surgery (if 100% sensitivity)	17%	5.8%

This illustration raises a number of issues. Firstly, the assumption that screening every two years with ultrasound would produce equivalent benefits to annual CA125 screening is likely to be inaccurate. It has been used to illustrate the greater sensitivity of TVS compared with CA125 based screening, which implies that a longer screening interval would detect the same proportion of cancers. The actual screening interval for TVS which would be equivalent to annual CA125 based screening is unknown. The shorter the screening interval, the greater the number of women with false positive tests, and the greater the costs of screening. The optimum screening interval depends on the rate of growth of ovarian cancer, and on the trade-off between costs, benefits and harms.

The number of women who might benefit from screening is shown to be small compared to the number of women who might suffer adverse effects. For every 1.5 extra survivors at 5 years, between 20 and 65 women who do not have ovarian cancer might undergo an operative procedure, and 300-350 would be told after initial screening that they required further tests, with the associated adverse psychological effects. However, it is possible that women undergoing surgery for benign conditions might derive benefit.

Researchers investigating screening for ovarian cancer have adopted an ad-hoc benchmark to define an 'adequate' screening test; it has been stated that a test which results in fewer than 1 in 10 operations finding ovarian cancer would be unacceptable in clinical practice.[117] This is an arbitrary figure, however, which has no empirical basis. In the above illustration, the maximum predictive value for the CA125 scenario was 17%, and for the TVS scenario, under 6%. These figures are based on the optimistic assumption that all cancers are detected at screening (ie 100% sensitivity), and may therefore be overestimates. However, the only other determinants of these estimates are the incidence of ovarian cancer, the frequency of screening and the false positive rate of the screening test. They therefore indicate fairly reliably, the maximum PPV likely for these tests in general population screening. Whether this is considered 'acceptable' involves a judgement about the likely benefits and risks; at present there is little information on which to base such judgements. Even if such information were available, individual women, clinicians and policy makers might form different views about what would be an acceptable PPV in practice.

Comparing this illustration with the situation for breast cancer screening, which may reduce mortality by up to 40% in screened women (as opposed to a 25% reduction in the population invited for screening), this results in 38 deaths averted per 100,000 screened women per year.[118] This is more than twice as many deaths prevented compared with ovarian cancer screening (assuming a 40% reduction in mortality), because of the higher incidence of breast cancer. If the costs of screening are similar, this suggests that ovarian cancer screening is likely to be less cost-effective than breast cancer screening, even under quite favourable assumptions. The same conclusion has been reached by other modelling studies.[36,114] Ovarian cancer screening, however, might need to be undertaken more frequently than the three yearly interval of the NHS breast screening programme, and this would further reduce its relative cost-effectiveness. Moreover, as indicated in Section 4.12 (Adverse effects of screening) many women will chose not to attend for repeated screening; in one study, even among a highly selected and motivated group of women at high risk because of their family history, 12% were against, or undecided about participation in further screening.[88]

It is therefore relevant to consider whether further research into screening for ovarian cancer should be considered a priority for the NHS, if it appears unlikely that general population screening could prove to be as cost-effective as screening for breast cancer, which has itself been a controversial use of NHS funds.[119] The following sections consider what impact further developments in ovarian cancer screening might have on its potential cost-effectiveness.

6.5 Developments in ovarian cancer screening

The overall impact of ovarian cancer screening depends on the balance of potential benefits, harms and costs. This balance will be more favourable if benefits can be maximised, and harms and costs minimised.

I. Treatment effectiveness

Any benefits of screening depend on the relative effectiveness (and cost-effectiveness) of early compared with late treatment. Increasing the effectiveness of treatment of screen-detected cancers may improve the cost-effectiveness of screening. Some of this may involve optimising the treatment received by women in the screening programme; estimates of potential mortality reductions above are based on the assumption that 5 year survival in early cancer is the same as that currently observed on a population basis, while 5 year survival rates in some trials in selected cases of early disease have exceeded 90%.[16] Conversely, however, any advances in treatment effectiveness for advanced cancer will reduce the potential for screening to improve outcomes.

II. Improvements to screening tests

a) Ultrasonography

Ultrasound screening appears to be quite sensitive in detecting ovarian abnormalities; however many screen-detected abnormalities are not malignant, but visualising them frequently leads to surgical intervention with a resulting high false positive rate. The challenge is therefore to improve the specificity of this test whilst retaining or improving sensitivity. Two methods under investigation are the role of colour Doppler imaging of ovarian blood flow, and the use of morphological classifications to distinguish benign and malignant lesions.

Despite the use of colour Doppler imaging in several prospective screening studies its role in screening is still not clearly defined, partly because technical developments in CDI imaging have meant continual changes to the cut-off points used to define abnormality. Several studies suggest that the use of CDI increases the specificity of screening, but it is unknown to what extent this may also reduce sensitivity. [35 36] It has been claimed that when used as an adjunct to grey-scale ultrasonography as an initial test, CDI can improve sensitivity by detecting small malignant lesions which are morphologically normal, on the basis of abnormal areas of blood flow.[120] However, these results have not been replicated, and there is considerable variation in the parameters which have been used to define CDI abnormalities and the results which have been obtained.[42] The ERTOCS study was unable to maintain a useful reduction in false positive rates by using CDI, and is no longer using information from CDI as part of the screening protocol. Colour Doppler equipment is also expensive, and its use would increase the costs of screening.

There is a need to characterise more reliably what it adds to screening by grey-scale ultrasound alone. The colour Doppler images being recorded as part of the ERTOCS trial will provide some answers, but will not demonstrate the effect of CDI used on all screened women. A reliable investigation of this question requires a blinded comparison on a cohort of women who are tested with and without colour Doppler imaging.

The specificity of ultrasound screening might also be improved by the development of precisely defined criteria to distinguish between abnormalities likely to be malignant and those likely to be benign and which need not be further investigated. However, there are difficulties with this strategy. Some abnormalities defined as 'benign' may in fact prove malignant, and this may lead to a reluctance to ignore them. This may result in large numbers of screened women being recalled for early rescreening, and those abnormalities which do not resolve may be operated on anyway. This is likely to increase the costs of screening, increase the anxiety and inconvenience of women and may not ultimately reduce the intervention rate.

The natural history of benign ovarian abnormalities is not fully understood, and there is some evidence that a proportion of benign ovarian neoplasms may undergo malignant change.[121] Furthermore, benign tumours may cause clinical problems in themselves. However, benign tumours which become malignant or become troublesome are likely to be in the minority, and interventions for such tumours may occur in women who would never otherwise have been troubled by them. However, this is not known and further research is needed in this area. Improving the specificity of ultrasound screening may therefore depend on a greater understanding of the risks and benefits of surgical intervention for apparently benign screen-detected lesions. Should the removal of benign tumours prove to reduce the subsequent risk of ovarian cancer, this will also increase the potential benefits of screening and reduce the potential negative outcome of unnecessary surgical intervention.

b) Tumour markers

For initial screening with tumour markers, the challenge is to improve the sensitivity, without compromising the high specificity which has been demonstrated. For the foreseeable future, any biochemical screening test for ovarian cancer will be based around CA125. Likely developments will centre around identifying further markers which might complement CA125 and increase its sensitivity, and the use of mathematical models using epidemiological information together with marker levels to define the risk of ovarian cancer.

The use of a model incorporating the rate of change of CA125 has been described,[122] and is being used in one of the RCTs.[109] The main drawback of this approach is the high proportion of women who must wait several weeks for repeat testing, before a decision is made as to whether they require a scan. This approach results in a higher false positive rate than use of only a single measurement of CA125, but the relative effect on sensitivity has not been published.[112]

A number of newer markers have been investigated to assess whether their use together with CA125 might increase the sensitivity of biochemical screening tests. Some encouraging preliminary results have been described for OVX-1 and M-CSF,[123] and OVX-1 was initially planned for use in one of the RCTs.[109] Unfortunately problems with the assay led to it being dropped from the screening protocol. Further evaluation of these markers is necessary.

A range of other markers has been investigated in screened cohorts: LASA, NB/70K, H-neu, and UGP.[75 124] The results obtained so far suggest that simple cut-off points have yet to be defined which might discriminate between women with early ovarian cancer and healthy women.

There is increasing interest in the development of complex algorithms for combining multiple marker results to increase discrimination. However, the capabilities of such models are still dependent on the development of tumour markers which discriminate well between women who have early ovarian cancer and women who do not.

The establishment of serum banks in large cohorts of women for whom there is accurate subsequent ascertainment of ovarian cancer incidence will facilitate the investigation of new markers as they are developed. This is proposed in all three of the RCTs currently in progress.

III: Reducing the harms of screening

Minimising the harms of screening depends partly on maximising the specificity of screening tests. However, methods to reduce the risks associated with a false positive test may also be important. There is a lack of published information on the nature and magnitude of such adverse effects, and therefore a need to characterise the harms of screening more precisely. These risks might be reduced by a clearer protocol for women referred for diagnostic interventions as a result of screening positive; or by the development of less invasive diagnostic techniques, such as greater use of laparoscopy. One prospective screening study used fine needle biopsy or cytology as a secondary test, and this might be worthy of further investigation.[64] Finally, if the removal of benign abnormalities proves to be beneficial, this will offset the potential hazards of intervention. Information relevant to this question should be provided by the RCTs in progress, and particularly the Barts trial which investigates the rate of gynaecological intervention in screened and control groups.

IV Reducing the costs of screening

Screening costs could potentially be reduced if some fixed costs could be shared with other screening programmes, for example breast screening. However, such a joint exercise may not be practical as it may increase the risk of confusion or error, given the large number of recalls involved. The opportunity to share fixed costs is also likely to be limited as the relevant facilities such as computers, facilities and staff have limited capacity and may already be fully committed to the breast screening programme.

One of the major determinants of screening costs is the frequency of screening, and therefore screening strategies which involve less frequent screening may prove more cost-effective. However, ultrasound screening, which may need to be performed less frequently, is also likely to be much more costly than CA125 screening. The most promising route to cost-effective screening may therefore lie in a screening method based on an initial blood test, which can be performed without the need for large

capital or training investment. This requires strategies to increase the sensitivity of such a screening method.

There is no obvious way to improve the cost-effectiveness of screening for the general population through improved test performance. The key issue is the low prevalence of ovarian cancer. One potential way forward is therefore to target screening towards women who are at increased risk of ovarian cancer.

6.6 Targeting screening on a higher risk population

In a higher risk population, a greater proportion of women will develop ovarian cancer. For any given test sensitivity, the same proportion of ovarian cancers will be detected at screening as in the general population, but the number of cancers will be greater due to the higher prevalence. Each woman with ovarian cancer has the same probability that screening will detect the cancer, and the same potential benefit compared with general population screening. However, because each woman screened has a higher risk of ovarian cancer, the likelihood of the test detecting cancer is greater for each woman. The likelihood of harm is however the same as in general population screening, assuming the same test specificity. Any benefits of screening depend on the benefit arising from early detection and treatment, and this has not been established for any risk group. Despite this, many centres in the UK are already offering screening as a service to some high risk women

Table 6.4 illustrates the potential effect on the outcomes of screening of selecting a population at higher risk. This illustration uses the 'TVS scenario' from table 6.3, applied to two different types of high risk population - women who have one relative with ovarian cancer, who are assumed to be at three times the risk of the general population, and women with two affected first degree relatives, who are assumed to be at ten times the risk of the general population. [28,31] The remaining assumptions are the same as for table 6.3.

The table shows that while the probability of harm is the same as for the general population, the probability of an individual benefiting from screening, if it is effective, is greater and therefore the balance of risks and benefits is more favourable. The number of additional survivors per 10,000 women screened rises in proportion to the increase in risk of ovarian cancer.

A number of the assumptions made for the general population may differ for the high risk population, however. The screening protocol proposed by the UKCCCR may be taken as typical of the approach currently adopted to screening this group.[113] This protocol proposes annual screening from age 25. This means that the average incidence of ovarian cancer will be lower than that assumed in table 6.4, reducing the relative advantage of screening a higher risk population. Secondly, the screening protocol is designed to maximise sensitivity at the expense of specificity, resulting in a higher false positive rate - 5% is suggested as acceptable in the study protocol. Maximising sensitivity may improve the proportion of cancers detected at an early stage and therefore, if screening is effective, result in a greater mortality reduction.

Table 6.4: Annual outcomes of screening in a hypothetical cohort of 10,000 *higher risk* women aged 50-64 assuming 40% mortality reduction and bi-annual TVS screening

	Three times risk (1 in 830 per year)	Ten times risk (1 in 250 per year)
Number of women participating in screening programme	10,000	10,000
Screening interval	Every 2 years	Every 2 years
Number of screening tests carried out per year	5,000	5,000
Number of women recalled for further assessment who do not have primary ovarian cancer per year	350 (7% of screens)	350 (7% of screens)
Number of women undergoing surgery who do not have primary ovarian cancer per year	65 (1.3% of screens)	65 (1.3% of screens)
Maximum number of cancers detected on screening per year (if 100% sensitivity)	12	40
Number of additional 5 year survivors per year	4.8	16
Predictive value of recall (if 100% sensitivity)	3.3%	10.3%
Predictive value of diagnostic surgery (if 100% sensitivity)	16%	38.1%

Table 6.5 incorporates these issues by assuming annual screening, a 60% reduction in mortality, a baseline incidence of 25 per 100,000 per year, a recall rate of 15% and a false positive rate of 5%.

Under these assumptions, both the benefits and the harms of screening are increased compared with the illustration in table 6.4. For women at moderately increased risk, the increased harms are large compared with the increased likelihood of benefit, and even for women at substantially increased risk the benefit:harm ratio is less favourable than for general population screening. This is due to the assumption of a much higher false positive rate, and illustrates the importance even in this group of maintaining the specificity of the screening process. However, women at significantly increased risk may have a higher level of anxiety about ovarian cancer, and therefore the value of being reassured by a true negative result may be more important to them. This means that sensitivity must be maximised to achieve a higher negative predictive value.

Screening a higher risk group means that fewer women must be screened for every case of ovarian cancer detected, and this may improve the cost-effectiveness of screening. However, if a screening programme were to be established for higher risk women, this would require a system to identify eligible women and call them for screening. This is much more complex than targeting screening by age, and in effect amounts to a two stage screening process. If screening is targeted at the very high risk groups, such identification requires the compilation of a detailed pedigree, which requires skill and time. The costs of this identification process would therefore greatly increase the total costs of such a screening programme, and might well result in

reduced cost-effectiveness compared to general population screening. The small numbers of women eligible for screening is likely to increase the average costs; it is estimated that there are around 50,000 very high risk women in England and Wales.[113] A screening programme for higher-risk women may be difficult to sustain, because public awareness that screening is being offered to some women could result in pressure for general population screening.

Table 6.5: Annual outcomes of screening in a hypothetical cohort of 10,000 *higher risk* women aged 25-75 assuming 60% mortality reduction and annual screening

	Three times risk (1 in 1300 per year)	Ten times risk (1 in 400 per year)
Number of women participating in screening programme	10,000	10,000
Screening interval	Annual	Annual
Number of screening tests carried out per year	10,000	10,000
Number of women recalled for further assessment per year who do not have primary ovarian cancer	1500 (15% of screens)	1500 (15% of screens)
Number of women undergoing surgery per year who do not have primary ovarian cancer	500 (5% of screens)	500 (5% of screens)
Maximum number of cancers detected on screening per year (if 100% sensitivity)	7.5	25
Number of additional survivors per year	4.5	15
Predictive value of recall (if 100% sensitivity)	0.5%	1.6%
Predictive value of diagnostic surgery (if 100% sensitivity)	1.5%	4.7%

Finally, only a very small proportion of ovarian cancers occur in such women with a very strong family history - perhaps 1%. The impact of such a screening programme is therefore likely to be very small on a population level, again limiting its cost-effectiveness.

Many women at significantly increased risk of ovarian cancer may be offered prophylactic oophorectomy. This reduces the risk of ovarian cancer but there remains a small residual risk of disseminated intra-abdominal carcinoma. There are also other potential adverse effects associated with surgery and subsequent reduced oestrogen levels. A full assessment of the benefits and harms of this strategy is beyond the scope of this review, but this is a potential alternative intervention to screening for this group. The vast majority of cancers in women at higher risk, like the general population, occur after the age of 40.[28]

7 REMAINING RESEARCH QUESTIONS

7.1 What are the benefits of screening for ovarian cancer?

The key question still to be answered is whether the use of currently available screening tests to screen for ovarian cancer in asymptomatic women will result in more benefit than harm, and at acceptable cost. This can only be investigated reliably in a RCT, which compares the mortality from ovarian cancer in the screened and control groups. Without such evidence, debate about the overall balance of costs, harms and benefits can only be based on information from models, whose assumptions may be unreliable. The trials in progress appear to be well designed and large enough to estimate the impact of screening on ovarian cancer mortality, although the results will not be available for at least 5 years and successful completion may be dependent on securing additional funding.

The trials however will only look at the effect of screening on ovarian cancer mortality, and not on the morbidity or quality of life experienced by women diagnosed with ovarian cancer. There is also the possibility that screening may have an impact on morbidity due to benign ovarian conditions, since many of these will be detected and removed as a result of screening. This effect may be either positive or negative, depending on the balance between operative morbidity and the morbidity of these conditions if treated conservatively. One of the RCTs will provide some information in the form of the numbers of operations undergone by screened and control groups.[109]

7.2 What are the harms of screening?

To judge the overall impact of screening on the health of a population requires information about the adverse effects of screening. These may include:

- operative morbidity in false positives undergoing diagnostic surgery
- anxiety in women initially screened positive or with equivocal results who are recalled for further assessment
- possible over-diagnosis and over-treatment of women with borderline tumours and benign conditions which might not otherwise cause any morbidity
- false reassurance in women who develop ovarian cancer following a negative screen result (interval cancers)

The published screening studies reviewed have not investigated these issues in detail, and have reported few data on adverse effects of screening, even though the design of these studies would allow assessment of these questions. There is, therefore, currently remarkably little published information about the consequences for women recalled or referred for diagnostic surgery who do not have ovarian cancer.

The RCTs in progress could provide some information relating to these issues. Data on complication rates is being collected, and it is important that this information is published in a timely manner to enable an assessment of the risks experienced by women entering these trials. On completion of follow-up, the RCTs will also allow

comparison of the incidence of ovarian cancer and borderline tumours in screened and unscreened groups.

However, the trials have not planned detailed investigations of the impact of screening on women who are recalled and referred unnecessarily. This may be particularly important in the Barts trial, where large numbers of women must wait for repeat CA125 levels, with up to five recalls for retesting before a final decision is made. It would seem sensible to consider the value of additional research as part of these trials to investigate these issues.

7.3 What is the overall impact and the cost-effectiveness of screening?

Assessing the overall impact of screening involves weighing up the probability of benefit and the probability of harm resulting from screening. The balance of benefits and harms which are judged 'acceptable' may vary between women, clinicians and policy makers, and between individuals. Research to increase knowledge of women's views of risk, and how they assess acceptable levels of risk, could be valuable in judging the circumstances under which screening might be considered worthwhile.

It is also important to assess the resources required for screening, to judge whether there may be more effective ways of deploying these resources. The Barts trial has so far not secured funding for an economic evaluation. Economic evaluation is an important consideration in deciding a policy for screening. It would therefore add value to the results of these trials to establish a collaborative economic analysis to enable an assessment of the relative cost-effectiveness of the different strategies.

7.4 Developing improved screening strategies

The potential impact of ovarian cancer screening might be improved in the following ways:

- improvements to the sensitivity and specificity of screening methods
- better understanding of the optimum management and natural history of screen detected benign conditions to reduce unnecessary intervention
- less invasive techniques for the diagnosis of ovarian cancer

With the results of RCTs some years away, it is important that the evaluation of the performance of potential new screening methods is carried out in such a way that the results are capable of being related to the results of these trials. The serum banks being established as part of these trials represent one way to achieve this, for serum based algorithms.

Research into the optimum management of screen detected benign lesions could be incorporated into screening trials. Such research could consist of randomised comparisons of active and conservative management of abnormalities where there is uncertainty as to the value of operative intervention. This might enable a reduction in

the false positive rate for ultrasound, if methods can be developed to characterise scan abnormalities which are at low risk of malignancy.

7.5 Screening women at higher risk of developing ovarian cancer

Until RCTs have been completed, the effectiveness of screening for ovarian cancer remains unproven, regardless of the underlying risk of ovarian cancer. Screening a higher risk group only changes the potential balance of benefit and harm - it does not establish benefit. Results from RCTs on the general population can be applied to a high risk population, so long as the natural history (i.e. the speed with which ovarian cancer develops and progresses) is similar in the two groups.

Research in this area should therefore concentrate on investigating issues which may be different in this group compared with the general population. These include:

- the natural history of ovarian cancer, including stage at diagnosis, histological type and grade
- the age-specific risk of developing ovarian cancer
- the psychological impact of risk assessment and screening in this group, who may have a different level of anxiety compared with the general population
- women's perception of risk, and the value they attach to knowledge of their individual risk, and the effect of presenting information about risk in different ways

These issues are most relevant to women at significantly increased risk, who have a history of more than one affected close relative. Investigation of the impact of screening in this group also requires investigation of methods of identifying higher risk women cheaply and accurately, and the effect of this on the cost-effectiveness of screening.

Finally, the possibilities of genetic testing to more accurately characterise risk in individuals are increasing as more mutations are discovered. Such testing is expensive and little is known about its consequences, or the purposes of testing if no effective interventions can be offered to the high-risk individual. This issue goes beyond the problem of screening for ovarian cancer, not least because many genetic mutations confer increased risk of cancer at more than one site, implying screening for several types of cancer. Research is needed into the impact of such screening on health outcomes at a population level, and the levels of demand for such services.

APPENDICES

APPENDIX 1: SEARCH STRATEGIES

1 Search strategy for screening studies

001 exp ovarian neoplasms/
002 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ab.
003 (ovar$ adj4 (oncolog$ or carcinoma$)).ab.
004 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ti.
005 (ovar$ adj4 (oncolog$ or carcinom$)).ti.
006 (adnexa$ adj mass$).tw.
007 1 or 2 or 3 or 4 or 5 or 6
008 exp mass screening/
009 (screen$ or test$ or imag$ or predict$ or surveillance).tw.
010 exp population surveillance/
011 (earl$ adj2 diagnos$).ab.
012 (earl$ adj2 detect$).ab.
013 (earl$ adj2 (treatment$ or therap$)).ab.
014 (earl$ adj2 diagnos$).ti.
015 (earl$ adj2 detect$).ti.
016 (earl$ adj2 (treatment$ or therap$)).ti.
017 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
018 7 and 17
019 limit 18 to human
020 letter.pt.
021 19 not 20
022 21

2 Search strategies for studies of adverse effects of surgery in false positives

001 oophorectomy.tw.
002 laparoscop$.tw.
003 cystectomy.tw.
004 diagnos$.tw.
005 ovariectomy/ae,px
006 exp hysterectomy/ae,mo,px
007 laparoscopy/ae,mo,px
008 laparotomy/ae,mo
009 exp anesthesia/ae,mo,px
010 1 or 2 or 3 or 4 or 5 or 6 or 7or 8.ti,ab,sh. or 9
011 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
012 exp postoperative complications/
013 exp intraoperative complications/
014 complication$.tw.

015 12 or 13 or 14
016 11 or 15
017 exp ovarian neoplasms/
018 16 and 17
019 11 and 15
020 17 and 19
021 20

3 Strategy for literature on adverse effects (psychological literature)

#1: SCREENING
#2: SCREENING in DE
#3: SCREENING-TESTS
#4: SCREENING-TESTS in DE
#5: DIAGNOSIS
#6: DIAGNOSIS in DE
#7: #2 or #4 or #6
#8: OVAR*
#9: CANCER*
#10: NEOPLASM*
#11: MALIGNAN*
#12: OVAR* near4 (CANCER* or NEOPLASM* or MALIGNAN*)
#13: OVAR*
#14: CARCINOMA*
#15: TUMO?R*
#16: OVAR* near4 (CARCINOMA* or TUMO?R*)
#17: #12 or #16
#18: #7 and #17
#19: FALSE
#20: POSITIVE
#21: FALSE POSITIVE
#22: FALSE
#23: NEGATIVE
#24: FALSE NEGATIVE
#25: #21 or #24
#26: NEOPLASMS
#27: NEOPLASMS in DE
#28: OVARIES
#29: OVARIES in DE
#30: #27 and #29
#31: #25 and #30
#32: #25 and #29
#33: ADVERSE
#34: EFFECTS
#35: ADVERSE EFFECTS
#36: #30 and #35

#37: #21
#38: #21 and #26
#39: #24 and #27
#40: #18 or #38 or #39

4 Search strategy for economic literature

#1 OVAR*
#2 explode OVARIAN NEOPLASMS/all subheadings
#3 explode MASS SCREENING/all subheadings
#4 #2 and #3
#5 explode COST (searched Costs and Cost Anaysis) /all subheadings
#6 #4 and #5
#7 COST-EFFECTIV*
#8 #4 and #7
#9 COST*
#10 BENEFIT
#11 COST* NEAR BENEFIT
#12 #4 and #11
#13 COSTS
#14 #4 and #13
#15 #6 or #8 or #12 or #14

APPENDIX 2: DATA EXTRACTION FORM

Reviewer.....

1. Study number(s) .....

2. Bibliographic details: First author.....
Journal.....
Year .....

Y/N

3. Inclusion criteria:
1. Subjects not suspected of having ovarian ca
2. Histological confirmation of ovarian ca
3. Tests performed prior to diagnosis
4. Subjects at risk of ovarian cancer (ie not selected to be disease free)

Continue if all four fulfilled

4. Country/region .....

5. Dates of recruitment .....

6. Methods of recruitment (tick any that apply):

self referred following publicity .....
referred by doctor .....
written invitation .....
other/comments.....
.....
.....

7. Inclusion/exclusion criteria:

Age .....
Menopausal status.....
Family history.....

Other important.....
.....
.....

8. Screening protocol:

Summary.....

a) Description of initial test(s) (performed on all subjects)

.....

.....

.....

.....

Definition of positive result (ie threshold for recall for further test(s))

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b) Description of follow-up test(s) if done:

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Definition of positive result (ie resulting in referral for definitive diagnosis)

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c) number of screening rounds completed and interval between them

.....

9. Description of reference standard for positive tests (ie how was the definitive diagnosis made: note if diagnosis/stage reviewed or carried out by one hospital/team; note if there was a protocol for diagnostic and staging procedures; note if the number of women undergoing different procedures is stated)

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10. Description of reference standard for negative tests (ie method and length of follow-up)

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.....

.....

.....

Results (give separately for each screening round if appropriate or state if results may come from different screening rounds; if different tests carried out on all women, give results separately for each test)

11. Number of women screened

Total.....

Age range.....

Number invited for screening.....

Numbers under 50/50+ (or nearest cut point given: state).....

Numbers pre/post-menopausal .....

Numbers with/without family history .....

Other information given.....

.....

.....

12. Number positive on initial tests (ie proceeding to further tests)

Total.....

Numbers under 50/50+ (or nearest cut point given:state...../.....

Numbers pre/post-menopausal ...../.....

Numbers with/without family history ...../.....

13. Number positive after further testing (ie proceeding to definitive diagnosis)

Total.....

Numbers under 50/50+ (or nearest cut point given:state...../.....

Numbers pre/post-menopausal ...../.....

Numbers with/without family history ...../.....

14. Dropouts.....

Uninterpretable tests.....

Equivocal tests.....

15. Number of ovarian cancers in screen positive women:

Total.....

Breakdown by stage I-IV.....

Numbers under 50/50+ (or nearest cut point given: state...../.....

Numbers pre/post-menopausal ...../.....

Numbers with/without family history ...../.....

16. Number of ovarian cancers in screen negative women:

Total.....

Breakdown by stage: I-IV.....

Breakdown by time since last screen: 1 year/2 year/more.....

Numbers under 50/50+ (or nearest cut point given: state...../.....

Numbers pre/post-menopausal ...../.....

Numbers with/without family history ...../.....

Completeness of follow-up:.....

17. Calculations (do separately for each screening round and each test if appropriate)

		Disease		
		+	-	
Test	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	a+b+c+d

a:

b:

c:

d (~c+d):

a+b:

c+d

a+c

b+d

a+b+c+d

a). Prevalence of screen detected cancer (a/a+b+c+d) per 100 000 .....

b) Sensitivity (a/a+c) .....

c) Specificity (d/b+d): note if estimated .....

d) False positive rate (b/b+d) .....

e) False negative rate (c/a+c) .....

f) PPV (a/a+b) .....

g) % of women recalled for further tests .....

h) % of women requiring surgery .....

Can calculations be performed for these subgroups: Age 50+.....

Post-meno.....

Family history.....

18. Quality check list

	Poor/not stated	Fair	good
a) Ref standard for positives (method and validity)			
b) Ref standard for negatives (method and completeness)			
c) Clarity of cut-off points			
d) Completeness of result reporting			
e) Drop-out rates (through the screening process)			
f) Description of study population with respect to important risk factors			
g) If tests performed at the same time, was there blinding?			

18. Further information:

a) Results of surgery in false positive women: nad.....

benign pathology.....

malignant pathology.....

b) Any women undergoing surgery outside screening protocol?.....

c) Reported surgical complications.....

d) information about psychological outcomes.....

.....

.....

.....

APPENDIX 3: STUDIES EXCLUDED FROM REVIEW OF TEST PERFORMANCE

Author	Reason for exclusion
Tay[125]	Study on women undergoing surgery for ovarian cysts
Grover[126]	Multiple publication of data in Grover 95[61]
Cane[124]	Retrospective analysis of tumour marker levels in women without ovarian cancer
Sato[127]	Retrospective analysis of bank of tumour markers
Sato[128]	Description of US imaging of ovaries - not a screening study
Pardo[129]	No surgical intervention to detect ovarian cancer in women with abnormal results
Campbell[130]	No data reported
Kuznetzov[131]	Not a screening study
Kuznetsov[132]	Not a screening study
van Nagell[133]	Multiple publication of data presented in DePriest 93[79]
Koboyashi[134]	Retrospective analysis of battery of tumour markers in a cohort of women
Koboyashi[135]	Multiple publication of Kobayashi 92a[134]
Kurjak[120]	Includes women presenting with clinical symptoms suspicious of ovarian cancer
Kurjak[41]	Includes women presenting with clinical symptoms suspicious of ovarian cancer
Ohmura[136]	A survey only
Einhorn[51]	No definitive intervention to diagnose ovarian cancer in women with abnormal test findings
Konno[137]	Multiple publication - same data as Sato 92b[67]
Schwartz[138]	Multiple publication of data presented in Schwartz 95[75]
Bourne[139]	Multiple publication of data reported in Bourne 93[35]
van Nagell[140]	Multiple publication of data reported in DePriest 93[79]
Osmers [141]	Multiple publication of Osmers 89[142]
Makarov[143]	Measurement of ovarian volume in healthy women - no intervention to detect ovarian cancer
Duda[144]	Included women who had presented with clinical symptoms of ovarian cancer
Campbell[145]	Retrospective analysis of data reported in Campbell 89[62]
Westhoff[146]	Measurement of CA125 levels in women assumed to be free of cancer - no intervention to detect ovarian cancer
Zurawski[52]	Follow-up study - no definitive intervention to detect ovarian cancer in women with abnormal findings
Kobayashi[147]	Multiple publication of data presented in Kobayashi 92a[134]
Kobayashi[148]	Retropsective analysis of tumour markers in healthy women and women with cancer
Koboyashi[149]	Not a screening study
Bhan[150]	Multiple publication of data presented in Campbell 89[62]
Besson[151]	Not a screening study

Osmers [142]	Included women who had presented with clinical symptoms of ovarian cancer
Author	Reason for exclusion
Higgins [152]	Multiple publication of data presented in van Nagell 90[81]
Alberico [153]	No surgical intervention to detect ovarian cancer in women with abnormal test results
Rodriguez [154]	A study comparing ultrasound findings with histology in women undergoing non-ovarian gynaecological surgery. No 'cut-off' point defined.
Goswamy [155]	Describes ovarian volume in healthy women -no intervention to detect ovarian cancer in women with abnormal findings
Schoenfeld [156]	Women referred for ultrasound examination for clinical indications (not asymptomatic
Oram [157]	Multiple publication of data reported in Jacobs 93[63]
Loskutova [158]	Not a study on screening for ovarian cancer, but on the outcomes of general clinical health checks for women. No screening protocol described
Loskutova [159]	Not a study on screening for ovarian cancer, but on the outcomes of general clinical health checks for women. No screening protocol described
Andolf [160]	Included women who presenting with clinical symptoms of ovarian cancer

APPENDIX 4: DETAILS OF PROSPECTIVE SCREENING STUDIES INCLUDED IN REVIEW OF TEST PERFORMANCE

Table 1a: Studies using grey-scale ultrasonography alone

Author **Year** **Country**	**Goswamy**[68] **1983** **UK**	**Andolf**[58] **1986** **Sweden**	**Millo**[57] **1989** **Italy**	**Campbell**[62] **1989** **UK**		
Test	TAS	TAS	TVS	TAS		
Screening protocol	Referred for diagnosis if abnormal morphology: entirely cystic, cystic with locules, cystic with solid areas, solid with irregular outline	Definition of positive results not given. Abnormal findings rescanned unless 'surgery immediately necessary'.	Recalled for repeat scan if pathological morphological features. Criteria for diagnostic intervention not stated	Recalled for repeat scan if hyper or hypoechogenicity, or irregular outline, or volume>20ml Referred for diagnosis if persistent abnormality Three screenings approx 18 months apart		
Study population	Post-menopausal women aged 39-78 Self referred	Women aged 40-70 years contacting gynae OPD for 'a variety of reasons'	Women aged 45+ or post-menopausal Mean age 54 Invitations to women attending cervical screening - about 50% uptake	Women aged over 45 or with family history (4%): (range 18-78, mean age 52) Self referred		
Number of women	1084	805	500	*Screen 1* 5479	*Screen 2* 4914	*Screen 3* 4201
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	Not stated	83 (10.3)	28 (5.6)	334 (6.1)	346 (7.0)	312 (7.4)
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	34 (3.1) 15 (1.4)	50 (6.2) 39 (4.8)	not clear 6 (1.2)	- 195 (3.6)	- 92 (1.9)	- 51 (1.2)
Cancers detected (rate per 1000) *total* *stage I invasive* *borderline*	 1 (0.9) 1 (0.9) -	 3 (3.7) - 2 (2.5)	 0 0 0	 2 (0.4) 1 (0.2) 1 (0.2)	 3 (0.6) 1 (0.2) 2 (0.4)	 0 0 0
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 6.7% 6.7%	 7.7 -	 - -	 1.0 0.5	 3.3 1.1	 - -
Cancers arising in screen negative women	not stated	not stated	not stated	0 at 1 year		
Follow-up of women screened negative	no information	no information	no information	86% complete follow-up 1 year after last scan: method not stated		
Sensitivity at 1 year **Specificity**	- -	- -	- -	100 96.5	100 98.2	100? 98.8
Details of outcome in women undergoing diagnostic procedures	14 benign disease	4 no abnormality, 32 benign disease	6 benign disease	4 malignant, 12 no abnormality, rest benign disease		
Details of diagnostic procedures	Laparotomy or laparoscopy	Laparotomy	not given	Laparotomy or laparoscopy; abnormal tissues removed for histology. Histology reviewed centrally and classified according to WHO criteria		

Table 1a (contd.) Studies using grey-scale ultrasonography alone

Author **Year** **Country**	**Demidov**[69] **1990** **Russia**	**van Nagell***[81] **1990** **US**	**DePriest***[79] **1993** **US**	**van Nagell***[65] **1995** **US**	**Tabor**[55] **1994** **Denmark**
Test	Ultrasound (not further specified)	TVS	TVS	TVS	TVS
Screening protocol	Women classified as positive on the basis of ovarian size - further details not given	Recalled for repeat scan if ovarian volume >18ml (premenopausal) Referred for diagnosis if persistent enlargement (premenopausal) or volume >8ml (postmenopausal) or complex or solid areas seen at any scan	First half of study: referred for diagnosis if ovarian volume >8ml or complex or solid areas Second half: referred if abnormality persisted on repeat scan	Recalled for repeat scan if ovarian volume >10ml (post-menopausal) or >20ml (pre-menopausal) or papillary projection into a cystic tumour. Referred for diagnosis if persistent abnormality	Recalled for rescan if ovarian volume >14ml (pre-menopausal) or >8ml (post-menopausal), or irregular outline or hyper/hypo-echogenicity. Referred for diagnosis if persistent, unless unilocular cyst <6cm dia. with smooth walls & no septations
Study population	Women aged 18 years and over Invited for screening (sampling frame not stated)	Women aged 40 years or older Mean age 45 Recruitment method not stated	Post-menopausal women aged 33-90 Mean age 60 Recruitment method not stated	Women aged either 50+ and post-menopausal or over 25 and with family history. Recruitment method not stated	Women aged between 46 and 65 invited to enter trial. 56% uptake
Number of women	11,996	1000	3220	8500	435
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	not stated	- 54 (5.4) -	not stated	not stated	54 (12.4) 54 (12.4) -
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	262 (2.2) 259 (2.2)	31 (3.1) 24 (2.4)	- 44 (1.4)	121 (1.4)	9 (2.1)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	 11 (0.9) 4 (0.3) -	 0 0 0	 3 (0.9) 2 (0.6) 0	 8 (0.9) 6 (0.7) 0	 0 0 0
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 4.2 1.5	 - -	 6.8 4.5	 6.7 5.0	 - -
Cancers arising in screen negative women	not stated	not stated	not stated	1 discovered incidentally (stage II) within 1 year	not stated
Follow-up of women screened negative	no information	Invited for rescreening at 1 year: details of follow-up not stated	Invited for rescreening at 1 year: details of follow-up not stated	Invited for rescreening at 1 year: details of follow-up not stated	no information
Sensitivity (at 1 year) **Specificity**	- -	- -	- -	88% maximum 98.7	- -
Details of outcome in women undergoing diagnostic procedures	248 benign disease	23 benign disease, 1 malignant disease	41 benign disease	112 benign disease, 1 malignant	9 benign disease
Details of diagnostic procedures	Surgery - no further details	Exploratory laparotomy with sampling of ovarian tumours	Exploratory laparotomy with removal and histology of ovarian tumours	Laparotomy or laparoscopy and removal and histology of ovarian tumour	Laparoscopy or laparotomy

* these three studies were carried out by the same research team and the study populations overlap: they are presented separately because each reports slightly different information. Note that the reported study protocol is slightly different for each study

Table 1b: Studies using ultrasonography with colour Doppler

Author **Year** **Country**	**Weiner**[72] **1993** **Israel**	**Kurjak**[70] **1994** **Croatia**	**Vuento**[56] **1995** **Finland**
Test	TVS and CDI	TVS and CDI	TVS and CDI
Screening protocol	Recalled for repeat scan if ovarian volume >20ml, or cyst or mass present, or low impedance intraovarian blood vessels Referred for laparotomy if persistent enlargement, complex cyst or low impedance blood flow Patients with simple cysts followed up with repeat scans	Recalled for repeat scans if 'enlarged' ovary or cyst >2.5cm or RI <0.4. Referred for diagnosis if persistent enlargement or cyst>5cm, or resistance index <0.4 at any scan. Morphology score also calculated but role in decisions not clear.	Recalled for repeat scan if ovarian volume >8ml or not uniformly hypo-echogeneic, or PI<=1 Referred for diagnosis if malignancy suspected. Other abnormalities followed up, except simple cysts <20mm dia.
Study population	Women with previous breast cancer referred from oncology clinic	Women aged between 40 and 71 years Mean age 45 Self referred	Women aged 56-61 eligible for mammography screening invited. Mean age 59 74% uptake
Number of women	600	5013	1364
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	 100 (16.7) 46 (7.7)	 424 (8.5) 316 (6.3)	 160 (11.7) 23 (1.7)
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	18 (3.0) 12 (2.0)	 38 (0.8)	5 (0.4) 5 (0.4)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	 3 (5.0) 1 (1.7) 0	 4 (0.8) 4 (0.8) 0 (0)	 1 (0.7) - 1 (0.7)
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 25.0 8.3	 10.5 10.5	 20.0 -
Cancers arising in screen negative women	not stated	not stated	0 at 1 year 1 at 2 years (stage 1)
Follow-up of women screened negative	Screen negatives recalled for rescan 1 year later- details of follow-up not given	no information	Women screened negative followed up through Finnish Cancer registry for 2.5 years
Sensitivity (at 1 year) **Specificity**	- -	- -	100 99.7
Details of outcome in women undergoing diagnostic procedures	8 benign disease, 1 malignant.	no information	4 benign disease
Details of diagnostic procedures	Exploratory laparotomy	A minority TAH and BSO, the rest had 'less major' procedures. 'Equivocal' results followed up at discretion of patients own doctor	3 laparotomies and 2 cyst aspirations.

Table 1c. Studies using grey-scale ultrasonography as an initial test with colour Doppler as a secondary test

Author **Year** **Country**	**Bourne**[35] **1993** **UK**		**Parkes**[36] **1994** **UK**
Test	TVS then CDI		TVS then CDI
Screening protocol	Rescanned if TVS showed areas of hyper or hypoechogenicity First 1000: referred for diagnosis if persistent morphological changes, unless volume reduced to <63% of initial scan	Rescanned if TVS showed areas of hyper or hypoechogenicity Second 601: referred for surgery if CDI showed pulsatility index <1 or morphology score >=5.	Recalled for CDI if ovarian volume more than 4 multiples of the age-specific median (pre-menopausal) or more than 3 multiples (post-menopausal). Referred for diagnosis if PI<1 and peak systolic velocity >10cm/s in an area of abnormal morphology, or ovary or cyst >5 cm dia., or very abnormal morphology
Study population	Women with a family history of ovarian cancer, age 17-79, mean 47 Self referred		Women aged 50-64 attending breast screening (uptake 74% for randomisation)
Number of women	1000	601	2953
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	Altogether: 909 (56.8)		not stated
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	52 (5.2) 52 (5.2)	9 (1.5) 9 (1.5)	15 (0.5) 14 (0.5)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	 3 (3) 2 (2) 1 (1)	 5.0 (3) 0 3.3 (2)	 1 (0.3) 1 (0.3) 0
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 5.8 3.8	 33.3 -	 7.0% 7.0%
Cancers arising in screen negative women	0 at 6-16 months 4 at 48 months - 1 stage II, 3 stage III	0 at 6-16 months	1 at 19 months: stage I
Follow-up of women screened negative	Patients contacted 6-16 months and asked about their health - 89% response rate Completeness of follow-up at 4 years not stated		no information
Sensitivity (at 1 year) **Specificity**	100 95.1	100 99.0	100 99.5
Details of outcome in women undergoing diagnostic procedures	7 no abnormality, 48 benign disease		13 benign disease.
Details of diagnostic procedures	57 had laparotomy and bilateral oophorectomy, four had laparoscopy. 8 further patients had prophylactic oophorectomy		8 underwent laparotomy, 2 laparoscopy and 4 cysts aspirated 10 further women referred for surgery outside the protocol

Table 1d: Studies using grey scale ultrasonography as an initial test, with other secondary tests

Author **Year** **Country**	**Sato** [67] **1992** **Japan**	**Schincaglia**[64] **1994** **Italy**	**Holbert**[71] **1994** **US**
Test	TVS then CT, MRI and combination of tumour markers (CA125, CA19-9, TPA)	TAS then aspiration cytology or biopsy	TVS then CA125
Screening protocol	Recalled for follow-up tests if TVS showed 'abnormal ultrasound findings' such as ovarian tumour >30mm dia, or ascites Referred for diagnosis if tumour >50mm or complex in nature, or if tumour marker algorithm abnormal	Initial scan: <9ml and cystic, repeat in 6 months. If enlarged, referred for biopsy/cytology 9-15ml: repeat in 3 and 6 months. If same size, referred for biopsy/cytology >15ml: referred for biopsy/cytology Biopsy/cytology: referred for diagnostic procedures if malignant cells seen, or enlarging complex or solid mass, or inadequate biopsy of complex or irregular mass, or cystic lesion recurring twice after aspiration	Recalled for repeat scan and CA125 if cystic ovaries present. Referred for diagnosis if cyst enlarging, or CA125>135U/ml, or patient choice
Study population	Women aged over 30 years Recruitment method not stated	Post-menopausal women aged 50-69 years attending a breast clinic	Post-menopausal women aged 30-89 attending for annual routine examinations
Number of women	15,282	3541	478
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	- 838 (5.5) ns	347 (9.8) 347 (9.8) 249 (7.0) underwent repeat scans, 98 (2.8) referred for biopsy/cytology	29 (6.1) 11 (2.3)
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	- 48 (0.3)	19 (0.5) 19 (0.5)	10 (2.1)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	1 'malignant', 1 'premalignant' ns ns	2 (0.6) 0 0	1 (2.1) 1 (2.1) 0
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	4.2 -	10.5 -	10.0 10.0
Cancers arising in screen negative women	not stated	none at 1 year	not stated
Follow-up of women screened negative	no details given	contacted at 12 months by questionnaire; also followed through cancer registry	Women screened negative called for repeat screening at 1 year; 6.7% follow-up
Sensitivity (at 1 year) **Specificity**	- -	100 99.5	- -
Details of outcome in women undergoing diagnostic procedures	46 benign disease	17 benign disease	9 benign disease
Details of diagnostic procedures	laparotomy	laparotomy	8 laparoscopic oophorectomy, 1 laparotomy and BSO, 1 TAH and BSO

Table 1e: Studies using CA125 followed by ultrasonography

Author **Year** **Country**	**Jacobs**[60] **1988** **UK**	**Jacobs**[63] **1993** **UK**	**Grover**[61] **1995** **Australia**	**Adonakis**[59] **1996** **Greece**
Test	CA125 followed by TAS	CA125 followed by TAS	CA125 followed by TAS or TVS	CA125 followed by TVS
Screening protocol	Recalled for TAS if CA125>=30U/ml Referred for diagnosis if ovarian volume >8.8ml	Recalled for TAS if CA125>=30u/ml. Referred for diagnosis if ovarian volume >8.8ml or non-uniform echogenicity or persistent morphological abnormality	Recalled for US and repeat CA125 if initial CA125 > 35U/ml or if 2 measurements >35U/ml (pre-menopausal) Referred for diagnosis if scan in post-menopausal women showed cyst, or enlarged or asymmetrical ovaries; in pre-menopausal women if cyst>6cm or with unusual features; also if CA125 level rising or very high	Recalled for TVS if CA125 >=35U/ml Referred for diagnosis if ovarian volume >18ml (premenopausal) or >8ml (postmenopausal), or hyper/hypoechogenicity or irregular outline
Study population	Postmenopausal women aged 45+ Mean age 54 Self referred	Postmenopausal women aged 45+ Median age 56 Self referred	Women aged over 40 or with a family history (3%) Median age 51 Self referred	Women aged over 45 Mean age 58 Self referred/invited
Number of women	1010	22,000	2550	2000
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	31 (3.1) 31 (3.1)	340 (1.6) 339 (1.5)	101 (4.0) 101 (4.0)	18 (0.9) 18 (0.9)
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	 3 (0.3)	41 (0.2) 41 (0.2)	8 (0.3) 8 (0.3)	14 (0.7) 14 (0.7)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	 1 (1.0) 1 (1.0) 0	 11 (0.5) 4 (0.2) 0	 0 0 0	 2 (1.0) 1 (0.5) 1 (0.5)
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 33.3 33.3	 26.8 9.8	 - -	 14.3 7.1
Cancers arising in screen negative women	none after 1 year	3 after 1 year 8 after 2 years (5 stage I, 3 stage III)	1 after 10 months (discovered on repeated CA125 testing)	None after 1 year
Follow-up of women screened negative	Negative screens followed up by annual postal questionnaire	Negative screens followed up by annual postal questionnaire: 98.7% response at 1 year, 57% at 2 years	Questionnaire at 12 months (results and completeness of follow-up not stated)	Negative screens followed up at second screening 1 year later. Completeness of follow-up not stated
Sensitivity (at 1 year) **Specificity**	100 99.8	78.6 99.9	- 99.7	100 99.4
Details of outcome in women undergoing diagnostic procedures	1 benign cysts and 1 no abnormality Those with negative ultrasound (44.6/1000) followed up with CA125 every 3 months for 1 year	25 benign pathology, 3 malignancies, 2 no abnormality	6 benign disease, 2 no abnormality	12 benign pathology
Details of diagnostic procedures	2 laparotomy, 1 not stated	Laparotomy or laparoscopy	3 laparoscopies, 5 laparotomies	Laparoscopy (2) or laparotomy (12)

Table 1e (contd.): studies using CA125 followed by ultrasonography

Author **Year** **Country**	**Bourne**[66] **1994** **UK**				
Test	CA125 and TVS then CDI: all subjects received both tests : retrospective analysis of effects of different levels of CA125 as an initial screen				
Screening protocol	Recalled for TVS: various values of CA125 Rescanned if TVS showed areas of hyper/hypoechogenicity First 1000: referred for surgery if persistent morphological changes, unless the volume had reduced to <63% of initial scan Next 601: referred for surgery if CDI showed pulsatility index <1 or morphology score >=5.				
Study population	Women with a family history of ovarian cancer, age 17-79, mean 47 Self referred				
Number of women	1601 (TVS)	1502 (CA125 available)			
	TVS:	*CA125 cut off point:*			
		20	*25*	*30*	*35*
Number positive on initial test (%)	1601 (100.0)	379 (25.2)	242 (16.1)	129 (8.5)	83 (5.5)
Number positive after further tests (%)	61 (3.8)	21 (1.4)	17 (1.1)	13 (0.9)	10 (0.7)
Cancers detected (rate per 1000):					
total	6 (3.7)	5 (3.3)	4 (2.7)	3 (2.0)	3 (2.0)
stage I invasive	2 (1.2)	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
borderline	3 (1.9)	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)
Probability of having ovarian cancer at diagnostic intervention (PPV:%)					
Any	9.8	23.8	23.5	23.0	30.0
Stage I invasive	3.3	9.5	11.8	7.7	10.0
Cancers arising in screen negative women	0	1	2	3	3
	4 arising 2-4 years after screening (not detected by US) 1 stage II, 3 stage III: one had CA125 >35U/ml, rest <20U/ml				
Follow-up of women screened negative	Negative screens contacted 6-16 months after screening to enquire about health. 89% response. Also asked to inform if cancer developed. Completeness of follow-up at 4 years not given				
Sensitivity (compared with ultrasound screening)	100	83.3	66.7	50.0	50.0
Specificity	96.6	98.9	99.1	99.3	99.5
Details of outcome in women undergoing diagnostic procedures	See results given in table 1b				
Details of diagnostic procedures	Most (58/62) underwent laparotomy and BSO Remaining 4 no abnormality on laparoscopy				

Table 1f: Studies using CA125 and ultrasonography

Author **Year** **Country**	**Akulenko**[80] **1992** **Russia**	**Karlan**[73] **1993** **US**	**Muto**[74] **1993** **US**	**Schwartz**[75] **1995** **US**
Test	CA125 and US and CA19-9 and REA	TVS and CDI and CA125	CA125 and TVS	CA125 and TVS and CDI
Screening protocol	No details given of criteria for recall or for referral for diagnosis	Tests repeated if adnexal mass>=5cm, abnormal ovarian architecture, RI<0.4, or CA125>35U/ml Referred for diagnosis if persistent abnormality on scan	Recalled for repeat testing if CA125>=35U/ml, or complex or large (>2cm) cyst (pre-menopausal), or any ovarian mass (post-menopausal). Referred for diagnosis if CA125 doubled or rose by >95U/ml or scan showed persistent mass	Recalled for repeat tests if CA125>35U/ml, or RI<0.5, or other abnormality Criteria for diagnostic intervention not stated
Study population	Women aged over 18 responding to an invitation to attend for a health check with a family history of breast, ovarian or endometrial cancer	Women aged over 35 with family history of ovarian, breast, endometrial or colon cancer Self or physician referred	Women aged 25 and over with a family history of ovarian cancer Self or physician referred	Women aged over 30 with a family history of ovarian cancer Median age 42.5 Self referred
Number of women	1003	597	384	247
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	not stated	115 (19.2)	89 (23.2) scan, 42 (10.9) CA125 55 (14.3) scan, 32 (8.3) CA125 34 (8.8) scan, 10 (2.6) CA125	not clear (initial screening not complete)
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	14	10 (1.7) - not clear whether follow-up completed	15 (3.9) scan, 8 (2.1) CA125 15 (3.9)	not clear 1 (0.4)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	1 (1.0) not stated	1 (1.7) 0 1 (1.7)	0 0 0	0 0 0
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	7.1 -	10.0 -	- -	- -
Cancers arising in screen negative women	not stated	not stated	not stated	not stated
Follow-up of women screened negative	no information given	Those testing negative recalled for second screen after 6 months- 25% follow-up completed	Women screened negative followed up with repeat screening; completeness of follow-up unclear	Women screened negative recalled for further screening at 6 months- no details of completeness of follow-up
Sensitivity (at 1 year) **Specificity**	- -		- -	- -
Details of outcome in women undergoing diagnostic procedures	11 benign disease, 2 no abnormality	8 benign, 1 malignant (endometrial carcinoma)	13 benign disease, 1 no abnormality, 1 malignant disease.	1 benign disease
Details of diagnostic procedures	no information	Laparotomy or laparoscopy and oophorectomy. 9 further women underwent prophylactic oophorectomy	8 TAH and BSO; 4 bilateral or unilateral oophorectomy, 1 cyst aspiration, 1 cystectomy, one laparoscopy. 4 women had surgery outside the protocol and 19 had prophylactic oophorectomy	1 woman underwent laparotomy for suspected malignancy - not clear if this is the only woman undergoing surgery as a consequence of the screening

Table 1f contd.: Studies using CA125 and ultrasonography

Author **Year** **Country**	**Belinson**[77] **1995** **US**	**Dorum**[76] **1996** **Norway**
Test	CA125 and TVS and CDI	CA125 and TVS
Screening protocol	Recalled for repeat test if CA125>35U/ml, or ovarian volume >18ml (pre-menopausal) or >8ml (post-menopausal), or abnormal morphology, or abnormal resistance index Criteria for diagnostic intervention not stated	Recalled for repeat TVS if simple uni- or bi-locular cyst >2cm dia. Recalled for repeat CA125 if >35U/ml Referred for diagnosis if tumour observed at first scan, or if persistent cyst on repeat scanning; or if CA125 >35u/ml at repeat testing
Study population	Women aged over 23 with family history of ovarian cancer Mean age 43 Self or physician referred	Women aged over 18 (mean 43 years), with two relatives with breast or ovarian cancer or one relative with breast and ovarian cancer Self or physician referred
Number of women	137	180
Number positive on initial test (%) **Number attending for further tests (%)** **Number still being retested (%)**	not clear	not stated
Number positive after further tests (%) **Number undergoing diagnostic tests (%)**	not clear 2 (1.5)	16 (8.9) 16 (8.9)
Cancers detected (rate per 1000): *total* *stage I invasive* *borderline*	 1 (7.3) 0 0	 7 (39) 0 (0) 3 (17)
Probability of having ovarian cancer at diagnostic intervention (PPV:%) *Any* *Stage I invasive*	 50.0	 44 -
Cancers arising in screen negative women	not stated	None
Follow-up of women screened negative	no information	56% returned for annual screening
Sensitivity (at 1 year) **Specificity**	- -	- -
Details of outcome in women undergoing diagnostic procedures	no information	9 benign conditions Further 13 women underwent oophorectomy as treatment for breast cancer; 2 had ovarian cancer not detected at TVS
Details of diagnostic procedures	1 laparoscopy and 1 laparotomy	14 laparotomy and oophorectomy; 2 laparoscopy

Table 1g: Studies using pelvic examination

Author **Year** **Country**	**Andolf**[58] **1986** **Sweden**	**Jacobs**[60] **1988** **UK**	**Grover**[61] **1995** **Australia**	**Adonakis**[59] **1996** **Greece**	
Test	PE followed by TAS	PE followed by TAS	PE followed by TAS or TVS	PE followed by TVS	
Screening protocol	Definition of positive results not given. Abnormal findings recalled for TAS. Criteria for diagnosis not stated	Recalled for TAS if palpable pelvic mass Referred for diagnosis if ovarian volume >8.8ml	Recalled for US if adnexal mass (post-menopausal) or abnormally large ovary (premenopausal). Referred for diagnosis if scan showed cyst, enlarged or asymmetrical ovaries (post-menopausal), or if cyst >6cm or with unusual features (pre-menopausal)	Recalled for TVS if palpable adnexal mass or inadequate PE. Referred for diagnosis if ovarian volume >18ml pre-menopausal. or >8ml postmen, or hyper/hypoechogenicity or irregular outline	
Study population	Women aged 40-70 years contacting gynae OPD for 'a variety of reasons'	Postmenopausal women aged 45+ Self referred	Women aged over 40 years or with a family history of ovarian cancer (3%)	Women aged over 45 age range 45-80, mean 58 self referred	
Number of women	805	1010	2550	2000	
Number positive on initial test (%)	13 (1.6)	28 (2.8)	40 (1.6)	*Abnormal PE*: 59 (3.0)	*Abnormal or ambiguous PE* 174 (8.7)
Number undergoing diagnostic tests (%)	8 (1.0)	11 (1.1)	10 (0.4)	27 (1.4)	33 (1.7)
Cancers detected (rate per 1000):					
total	0	1 (1.0)	0	1 (0.5)	2 (1.0)
stage I invasive	0	1 (1.0)	0	1 (0.5)	1 (0.5)
borderline	0	0	0	0	1 (0.5)
Probability of having ovarian cancer at diagnostic intervention (PPV:%)					
Any	-	9.1	-	3.7	6.1
Stage I invasive		9.1	-	3.7	3.0
Cancers arising in screen negative women	3 detected by TAS	none	none	1 (found on CA125 testing)	0
Details of outcome of women undergoing diagnostic procedures	8 benign disease	8 benign cysts and 1 no abnormality, 1 declined surgery	9 benign disease, 1 no abnormality	27 benign pathology, 1 malignant, 3 no abnormality	
Details of diagnostic procedures	Laparotomy or laparoscopy	Not given	Laparotomy or laparoscopy	Laparoscopy or laparotomy	

APPENDIX 5: DETAILS OF MODELLING STUDIES

Author	Aim and design of study	Population Screening procedure and assumptions	Assumptions about benefits and harms of screening	Cost data	Findings Comments
Westhoff[116]	To illustrate the potential effect of screening on ovarian cancer mortality	Cohort of women screened annually between the ages of 45-74 80% sensitivity of test; all screen-detected cancers assumed to be at stage I Test specificity varied	Stage specific survival rates taken from observed survival rates in the US; benefits calculated as the number of extra 5 year survivors per year No account taken of potential harms of screening	None	6000 screening tests needed to produce one extra 5 year survivor (if 80% of cancers diagnosed at stage I) Screening test specificity of 98% results in 50 positive test results per cancer detected Comment: similar methodology to Parkes Cannot calculate number of life years gained
Parkes[36]	To illustrate the potential effect of screening on ovarian cancer mortality Comparison of expected cost-effectiveness of ovarian cancer screening compared with breast and cervical	Cohort of women screened every three years between the ages of 50 and 64 Mortality reduction at 5 years estimated on the basis of varying proportions of cancers diagnosed at stage I in the screened population	5 year survival at stage I -75%; at later stages - 16% Proportion of cancers diagnosed at stage I in unscreened population - 33% Life expectancy of each additional survivor at 5 years - 19.3 years No account taken of potential harms of screening	Cost per screen assumed to be £20 for ovarian cancer and same for breast cancer	If screening increases proportion of stage I cancers to 80%, mortality reduction of 43% at 5 years. Cost per life year saved about twice that of breast cancer screening and a little less than that of cervical screening. Comment: cost-effectiveness comparisons depend on screening interval of 3 years which may be over-optimistic
Schapira[114]	To illustrate the net benefit in terms of average life expectancy resulting from screening for ovarian cancer, using a decision analysis model	Cohorts of 40 year old and 65 year old women resident in the USA Screening occurs once only at age 40 or age 65. Screening test sensitivity 45% for early disease and 81% for late disease. 50% of prevalent cases in early stage. Test specificity 99.95%	Survival from early disease 26.8 years at age 40, 18.3 years at age 65; survival from late disease 3.4 and 2.7 years respectively Probability of death following diagnostic laparotomy 0.2% at age 40 and 1.5% at age 65	None	Screening increased average life expectancy by one third of a day in 40 year olds and by three quarters of a day in 65 year olds. Screening reduced average life expectancy at a screening specificity of 98.5%. Comment: the probability of death after laparotomy is probably an over-estimate and is based on mortality from staging laparotomies. Use of average benefit makes the size and distribution of benefits and harms unclear

Author	Aim and design of study	Population Screening procedure and assumptions	Assumptions about benefits and harms of screening	Cost data	Findings Comments
Skates[115]	To illustrate potential benefit of CA125 screening using a stochastic model	Annual CA125 screening for women aged between 50 and 75. Models the detection of ovarian cancer assuming CA125 levels rise exponentially with time and that a level over 35 u/ml results in detection. Natural history modelled on the basis of clinical opinion - stage I assumed to last 9 months on average.	Survival following diagnosis based on observed stage-specific survival curves No account taken of potential harms of screening	None	44% of cases detected at an earlier stage; 7.7 years of life gained for each case detected at screening, and 3.4 for each ovarian cancer diagnosed Comment: use of stochastic simulation enables more sophisticated modelling of the dynamic nature of cancer development. Gains predicted are lower than Parkes and slightly greater than Schapira, but of the same order of magnitude
Urban [107]	To compare the relative cost-effectiveness of different screening strategies, measured as cost per life year saved	Screening women aged 50-79 with a variety of strategies. CA125 model similar to that developed by Skates; TVS model based on reported false positive rates and sensitivity equivalent to 88% for annual screening	Survival post diagnosis based on currently observed stage specific survival curves Probability of death at laparoscopy assumed to be 0.1%; this is combined with benefits to give average life years saved with each strategy	Based on charges in the US: $40 for CA125, $150 for TVS, and $3000 for laparoscopy. Treatment costs also incorporated	Found that annual CA125 followed by TVS if level elevated or rising was the most cost-effective strategy - it resulted in fewer life years saved compared with annual TVS but the cost per LYS was less. This finding was robust over a range of sensitivity analyses Comment: the total life years gained was equivalent to only about one year for every case of ovarian cancer. Charge data may be inaccurate compared with true costs.

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